UNIVERSITY OF ALBERTA

Synthesis and Anti-Cancer Activity of Anthracycline Mimetics

by

Eric Fan

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ABSTRACT

Anthracycline antibiotics are effective cancer chemotherapeutics. The aromatic portion of these drugs intercalates between DNA base pairs and the carbohydrate moiety is bound in the minor groove. When bound to DNA, these compounds inhibit the action of topoisomerases.

This project involves the development of new anthracycline mimetics that could potentially bind to DNA and inhibit topoisomerases. Two simplified aromatic aglycones were prepared along with five monosaccharide donor cores. The synthesis of the 1,2,3,4-tetrahydronaphthyl core was achieved in ten steps from anthranilic acid in 13% yield, while the 1,2,3,4-tetrahydoanthranyl core was obtained in 14 steps from 1,2,4,5-tetrabromobenzene in 4% yield. Five sugar donors were prepared from L-rhamonse and glycosylation was carried out by activation of $AgPF_6$ and 2,6-di-*tert*-butyl-methylpyridine. The nine compounds were assayed for cytotoxicity against the MCF-7 cancer cell line, and the anthranyl compounds showed better potency than the naphthyl compounds, while changes in the monosaccharide cores had no influence on activity.

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Dedicated to My Loving Parents and My Dearest Sister

TABLE OF CONTENTS

Chapters Page

1. Introduction.....1

1.1. Overview.....2

1.2. Topoisomerases I and II.....4

1.3. Topoisomearse Inhibitors.....8

1.4. Mechanism of Action and Cytotoxic Effect of Anthracyclines.....15

1.5. Novel Anthracyclines.....21

1.6. Research Overview.....30

2. Preparation of Anthracycline Mimetics. Synthesis of 1,2,3,4,-Tetrahydro-naphthyl, 1,2,3,4-Tetrahydro-anthranyl Cores and Thioglycoside Donors and their Glycosylation Reactions.....31

2.1. Background.....32

2.2. Synthesis of the 1,2,3,4-Tetrahydro-naphthyl Core.....36

2.3. Synthesis of the 1,2,3,4-Tetrahydro-anthranyl Core.....50

2.3.1. Resolution of 1,2,3,4-Tetrahydro-anthranyl Core.....57

2.4. Synthesis of the Monosaccharide Donors.....60

2.4.1. Synthesis of Monosaccharide Donor **2.36**.....61

2.4.2. Synthesis of Mononsaccharide Donors **2.37** and **2.38**.....63

2.4.3. Synthesis of Mononsaccharide Donors **2.39** and **2.40**.....66

2.5. Synthesis of 1,2,3,4-Tetrahydro-naphthyl Glycosides.....67

2.6. Synthesis of 1,2,3,4-Tetrahydro-anthranyl Glycosides.....75

2.7. Biological Evaluation and Cytotoxicity Assays.....81

2.8. Conclusion.....83

3. Experimental Procedures.....84

3.1. General Methods.....85

3.1.1. Cytotoxicity Assay.....87

3.2. Procedures for the Synthesis of 1,2,3,4-tetrahydro-naphthyl Core.....88

3.3. Procedures for the Synthesis of 1,2,3,4-Tetrahydro-anthranyl Core.....101

3.3.1. Procedure for the Resolution of 1,2,3,4-Tetrahydro-anthranyl Core.....112

3.4. Procedures for the Preparation of Monosaccharide Donors.....116

3.5. Preparation of 1,2,3,4-tetrahydro-naphthyl and 1,2,3,4-Tetrahydro-anthranyl Glycosides.....137

3.5.1. General Procedure for the Glycosylation of 1,2,3,4-Tetrahydro-naphthyl and 1,2,3,4-Tetrahydro-anthranyl cores. 137

3.5.2. General Procedure for the Removal of Acetate Group of 1,2,3,4-Tetrahydro-naphthyl and 1,2,3,4-Tetrahydro-anthranyl Glycosides.....149

3.5.3. General Procedure for the Reduction of 1,2,3,4-Tetrahydro-naphthyl and 1,2,3,4-Tetrahydro-anthranyl Azido Glycosides.....153

Bibliography.....162

LIST OF TABLES

Table		Page
2.2.1.	Conditions Examined for the Preparation of Alcohol **2.17**	40
2.2.2.	Summary of Addition Reaction Conditions for Ketone **2.18**	45
2.2.3.	Reaction Conditions Used for Ozonolysis of Alkene **2.19**	47
2.3.1.	Summary of Nickel/(*R*)-BINAP Catalyzed Reactions of Oxatricyclic Alkene	54
2.5.1.	Summary of Glycosylation Reactions for the Tetrahydro-naphthyl Core	69
2.6.1.	Summary of Glycosylation Reactions for the Tetrahydro-anthranyl Core	76

LIST OF FIGURES

Figure		Page
1.1.1.	Structure of Zarnestra	3
1.2.1.	Schematic Model for Topoisomerase I-mediated DNA Cleavage and Religation	5
1.2.2.	Topoisomerase I Catalyzed DNA Cleavage and Religation Mechanism	6
1.2.3.	Schematic Model for Topoisomerase II-mediated DNA Cleavage and Religation	7
1.3.1.	Structure of Topotecan	8
1.3.2.	Structures of Anthracyclines Clinically Used in the Treatment of Cancer	9
1.3.3.	Crystal Structure of Daunomycin-DNA complex. The Anthraquinone Moiety Intercalates Between GC Base Pairs, and the Amino Sugar sits in the Minor Groove	12
1.3.4.	ORTEP Representation of Two Anthracycline Compounds Bound to d(CGATCG)	13
1.3.5.	Structures of Anthracycline Analogs Used in Computational Modelling Study	14
1.4.1.	Formation of DNA-drug Adduct Mediated by Formaldehyde	18

1.4.2. Structure of Anthracycline-DNA Adduct via Aminal (N-C-N) Linkage. (A) Doxorubicin-DNA Adduct and Stabilization by Second DNA Strand through Confirmation of 2D NMR Study....19

1.5.1. Structures of Doxorubicin, Epirubicin, and Idarubicin....22

1.5.2. Structure of Idarubicin Dissacharide Analogs....23

1.5.3. Structures of Morpholinyl and Cyanomorpholinyldoxorubicin....24

1.5.4. Structures of Pirarubicin and Aclacinomycin....25

1.5.5. Structures of MEN10755 and MAR70....26

1.5.6. Annamycin and 4-Demethoxy Analogues Anthracycline....27

1.5.7. Structure of WP744....28

1.5.8. Disaccharide Daunorubicin Analogs Synthesized by Wong and Co-workers....28

1.5.9. Structure of Doxoform and Daunoform....29

1.6.1. Structure of Anthracycline Analogs that were Synthesized....30

2.1.1. Structures of the 1,2,3,4-Tetrahydro-naphthyl **2.11** and 1,2,3,4-Tetrahydro -anthranyl **2.12** Aglycone Cores....35

2.2.1. Single X-Ray Crystal Structure of Alkene **2.19**....46

2.4.1. *J* values for H-1 and H-3 of Ribose and Arabinose Compounds....65

2.5.1. Proposed Mechanism for the Formation of the β Product of **2.54**....71

2.6.1. Compounds Used for Biological Screening....79

2.7.1. Schematic of PROMEGA CellTiter 96® AQ_{ueous} One Solution Reagent Cell Proliferation Assay....80

2.7.2. Cytotoxicity Data for Target compounds dosed at 100 μM.....81

3.1.1 Structural Assignments of Compounds.....85

3.2.1. HPLC Trace of (*S*)-(1H,2H)dihydronaphthalen-1-ol.....88

3.3.1. HPLC Trace for 1-Hydroxy-3,4-dihydro-anthracene.....103

LIST OF SCHEMES

Scheme		Page
1.3.1.	Biosynthetic Pathway from Malonyl-CoA and Propionyl-CoA Precursors to Anthracycline Antibiotics	10
1.4.1.	Cascade Reactions in DNA-drug Adduct Formation	16
2.1.1.	Synthesis of Idarubicinone Using Homophthalic Acid	32
2.1.2.	Synthesis of Idarubicinone from L-Rhamnose	33
2.1.3.	Synthesis of Idarubicinone from Carboxylic Acid Derivatives	34
2.2.1.	Synthesis of the 1,2,3,4-Tetrahydro-naphthyl Core Using Jacobsen's Catalyst and Sodium Molybdate	36
2.2.2.	Preparation of 1,2,3,4-Tetrahydro-naphthyl Target from (*S*)-(1H,2H)-dihydronaphthalen-1-ol	37
2.2.3.	Retrosynthesis of 1,2,3,4-Tetrahydro-naphthyl Core	38
2.2.4.	Preparation of Secondary Alcohol **2.17**	39
2.2.5.	Preparation of Ketone **2.18**	42
2.2.6.	Various Methods Employed in the Addition Reaction	43
2.2.7.	Optimized Reaction Conditions for Grignard Addition Reaction	46
2.2.8.	Final Sequence Towards Naphthyl Target	48
2.2.9.	Synthetic Sequence for the 1,2,3,4-Tetrahydro-naphthyl Core	49
2.2.10.	Hydrogenation of (*S*)-(1H,2H)-dihydronaphthalen-1-ol **2.21**	49

2.3.1. Retrosynthesis of the 1,2,3,4-Tetrahydro-anthranyl Core.....50

2.3.2. Initial Attempts for the Preparation of Oxatricyclic Alkene **2.22**.....51

2.3.3. Improved Synthesis of Oxatricyclic Alkene **2.22**.....52

2.3.4. Preparation of Alcohol **2.26**.....53

2.3.5. Attempted Resolution of Alcohol **2.26** with *S*-acetyl-mandelic Acid.....55

2.3.6. Preparation of Ketone **2.29**.....55

2.3.7. Final Sequence Towards Compound Mixture **2.32**.....56

2.3.8. Resolution of Compound **2.12** with *R/S*-acetyl-mandelic Acids.....58

2.3.9. Synthetic Scheme for the 1,2,3,4-Tetrahydro-anthranyl Core.....59

2.4.1. Retrosynthesis of Monosaccharide Donors.....60

2.4.2. Preparation of Building Block Glycal.....61

2.4.3. Synthesis of Thioglycoside **2.42**.....62

2.4.4. Synthesis of Monosaccharide Donor **2.36**.....63

2.4.5. Preparation of **2.48**.....64

2.4.6. Separation of the Arabinose and Ribose Isomers.....65

2.4.7. Preparation of Monosaccharide Donors **2.36** and **2.37**.....66

2.4.8. Preparation of Monosaccharide Donors **2.39** and **2.40**.....66

2.5.1. Initial Glycosylation Reactions Using AgOTf and NIS.....67

2.5.2. Glycosylation Reactions Using $AgPF_6$ and DTBMP for the Naphthyl Core.....68

2.5.3. Deprotection and Reduction of Azido Group in 1,2,3,4-Tetrahydro-naphthyl Glycosides.....72

2.5.4. Reduction of Azido Group in 4-*O*-benzyl Analogs.....73

2.5.5. Synthetic Sequence for Compound **2.66**.....74

2.6.1. Glycosylation Reactions Using $AgPF_6$ and DTBMP for the Anthranyl Core.....75

2.6.2. Deprotection and Reduction of Azido Group in 1,2,3,4-Tetrahydro-anthranyl Glycosides.....78

LIST OF ABBREVIATIONS

Abbreviation	Full Name of Compound
Ac	Acetyl
Ac_2O	Acetic anhydride
aq	Aqueous
AgOTf	Silver trifluoromethanesulfonate
BINAP	2,2'-Bis(diphenylphosphino)-1,1'binaphthyl
Bn	Benzyl
Bu	Butyl
Bz	Benzoyl
cat.	Catalytic
COD	Cyclooctadiene
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMF	*N,N'*-Dimethylformamide
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
EDC	*N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide

Et	Ethyl
IBX	2-Iodoxybenzoic acid
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
Ms	Methanesulfonyl
NIS	*N*-Iodosuccinimide
NMO	4-Methylmorpholine *N*-oxide
Ph	Phenyl
PMB	4-Methoxybenzyl
Salen	Salisaldehyde ethylenediamine
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
Tf	Trifluoromethanesulfonyl
Tf_2O	Trifluoromethanesulfonic anhydride
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Tol	Tolyl
TPAP	Tetrapropylammonium perruthenate

CHAPTER 1

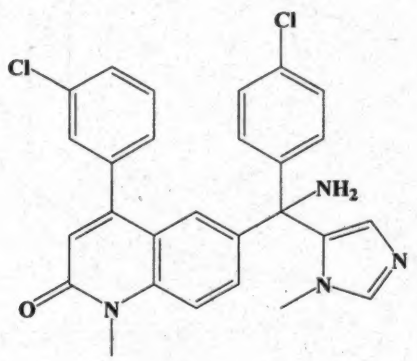
INTRODUCTION

1.1. Overview

All living organisms thrive to achieve the same objective, and through an evolutionary perspective this goal is realized when these organisms are able to successfully replicate themselves through the transfer of their own genetic information to a new generation of offspring. In the process of mitosis, this cellular activity can only be effective, if it is are able to perform without any interruptions. Mutations from a single nucleotide base during replication can lead to disruption in normal cellular activities. Genetic mutations such as the exchange of one nucleotide base for another may disrupt the proper function of cellular processes. The carcinogen known as aflatoxin B, found in mould cells that grow on food, causes a mutation in the tumor-suppressor gene *p53* and it is believed that this type of mutation is linked to the formation of lymphomas, sarcomas, and melanomas.[1,2,3] Aflatoxin M1 has also been shown to intercalate into DNA and alkylate the DNA base pairs.[2,3] Cancer is a genetic disease because it is linked to alterations within a specific gene. Due to these genetic changes, cancer cells proliferate uncontrollably leading to the formation of a malignant tumor.

Cancer impacts all aspects of human lifestyle, and major efforts have been devoted to treating this malicious disease. Current methods used in the treatment of cancer, such as chemotherapy and radiation, have provided limited success in targeting between malignant cells and normal cells.[4] Several new strategies are being evaluated in targeting tumor cells: immunotherapy, gene therapy, inhibition of angiogenesis, and the inhibition of cancer promoting proteins (i.e. topoisomerases).[5] In immunotherapy, a person is treated by exposure to tumor-specific antigens, therefore leading to an immune response, which releases antibodies targeted towards cancer cells.[6] For gene therapy, the

introduction of a tumor-suppressor gene may lead to changes in the genotype of the cancer cell, thereby altering its normal cellular acitivities.[7] Anti-angiogenesis drugs such as endostatin are used to prevent the formation of blood vessels, which in turn deprives the cancer cell of rich nutrients and fresh oxygen. The hyperactivity of a particular enzyme or a protein within a cancerous cell can lead to abnormal growth of tumor cells. In the case of the protein Ras (responsible in activating a signaling pathway leading to cell growth and cell division), another enzyme, farnesyltransferase (FT), is needed in order for this protein to function properly. The drug, Zarnestra™ **1.1**, developed by Johnson & Johnson, is an inhibitor of FT and has recently been shown to be effective in the treatment of acute myeloid leukemia.[8] Therefore, inhibitors of other enzymes involved in cell division could also be used in the treatment of certain forms of cancer, and efforts toward the identification of new inhibitors of one class of such enzymes, the topoisomerases, and are the subject of this thesis.



1.1

Figure 1.1.1. Structure of Zarnestra.™

1.2. Topoisomerases I and II

Topoisomerases are enzymes that mediate the topological state of DNA inside the cell. They facilitate the unwinding of DNA providing access to the genetic information inside.[9] Topoisomerases are involved in DNA replication and transcription through unlinking and reverse supercoiling of DNA. These unwinding events lead to the opening of the double helix, which allows other enzymes such as DNA and RNA polymerase to function. Two subfamilies of the enzyme, Topoisomerase I (Top I) and topoisomerase II (Top II), are of interest in our research. These enzymes differ in their cleavage and religation processes. Topoisomerase I promotes the cleavage of a single strand of double stranded DNA and functions by nicking one of the strands of the DNA double helix. The nicked strand will then twist around the other strand and religate the broken strand to yield an unwound structure. This method of uncoiling does not rely on the use of ATP; instead, the torque that is present in the DNA drives this process (Figure 1.2.1.).[10] Eukaryotic topoisomerase I is a monomeric protein that is comprised of 765 amino acids.[11] The active region in which catalysis occurs is at the C-terminal region of and it contains the active site that includes a catalytic tyrosine residue.[12,13]

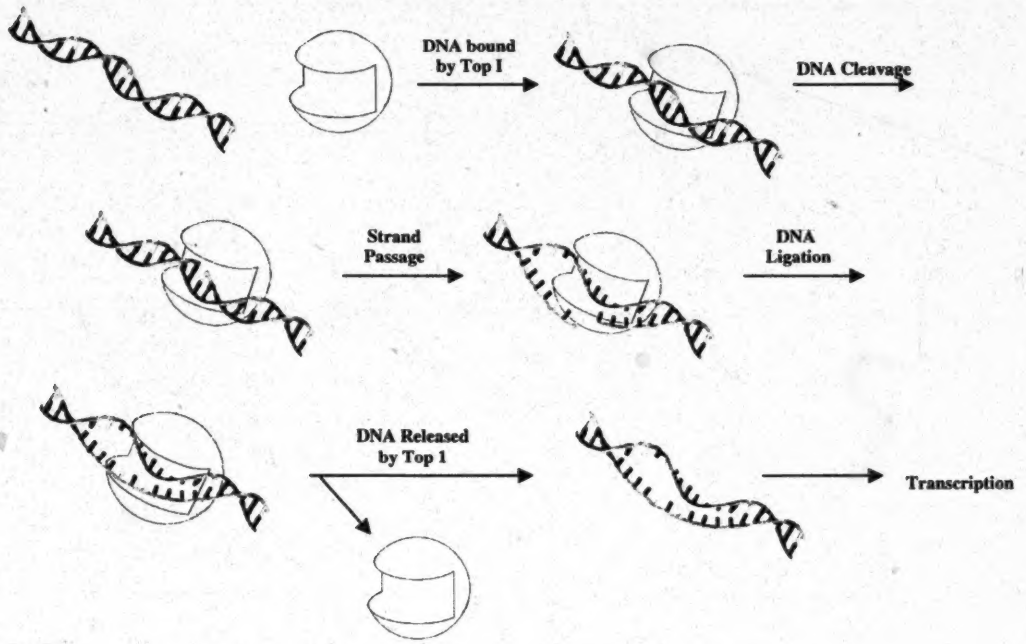


Figure 1.2.1. Schematic model for Topoisomerase I-mediated DNA Cleavage and Religation.[10] (adapted from Champoux, J. J.)

The mechanism of catalysis of topoisomerase I DNA cleavage occurs via nucleophilic attack by the oxygen of the tyrosine residue (Tyr^{723}) onto the phosphate group of the DNA strand. This results in the formation of a phosphodiester link between the tyrosine residue and the 3' phosphate, which cleaves the DNA. The reverse process, religation, can be envisioned by the attack of the 5' hydroxyl onto the phosphodiester link of the enzyme-bound substrate, thus liberating the enzyme and reconnecting the DNA fragment (Figure 1.2.2.).[10]

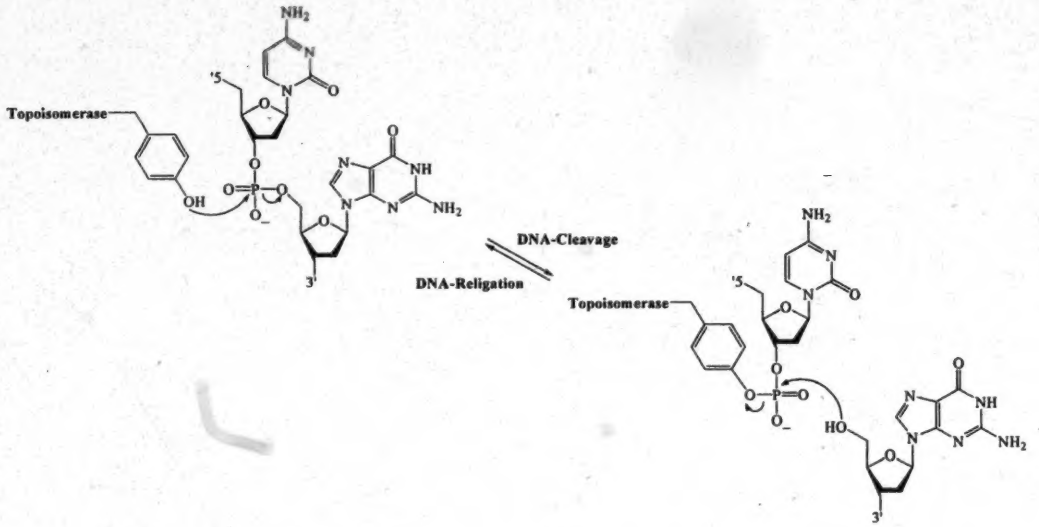


Figure 1.2.2. Topoisomerase I Catalyzed DNA Cleavage and Religation Mechanism.[10]

Type II topoisomerase cleaves both strands of the double-stranded DNA helix simultaneously. The breaking of both strands allow the ends of the DNA to be separated, and a second DNA duplex is passed through the break. Type II topoisomerase plays an important role in chromosomal segregation/condensation and in manipulating DNA superhelicity.[14] Eukaryotic topoisomerase II is a dimer, and its mode of action is similar to that of topoisomerase I. Two tyrosine residues, one from each half of the dimeric enzyme, work simultaneously to cleave one DNA duplex (the T-segment). The phenolic oxygen of the tyrosine residues form phosphodiester linkages at the 5' ends of the DNA forming a pair of 3' adducts, analogous to that shown in Fig. 1.2.2. The enzyme-DNA complexes and the fragmented DNA move away from one another, creating a small channel through which another double-stranded DNA (the G-segment) is transported. Once the DNA segment has passed through, the enzyme–mediated channel closes and a

transesterification between the 3' hydroxyl groups and the phosphotyrosyl linkage of the DNA-enzyme complex restores the DNA strand and leads to the release of the enzyme (Figure 1.2.3.).[15] This mechanism requires the enzyme to undergo numerous conformational changes that support the notion that ATP is needed for binding and hydrolysis to drive a full reaction cycle.[16] Since topoisomerases are involved in the cellular division process, inhibitors of Top I and II enzymes are ideal targets for anticancer agents.

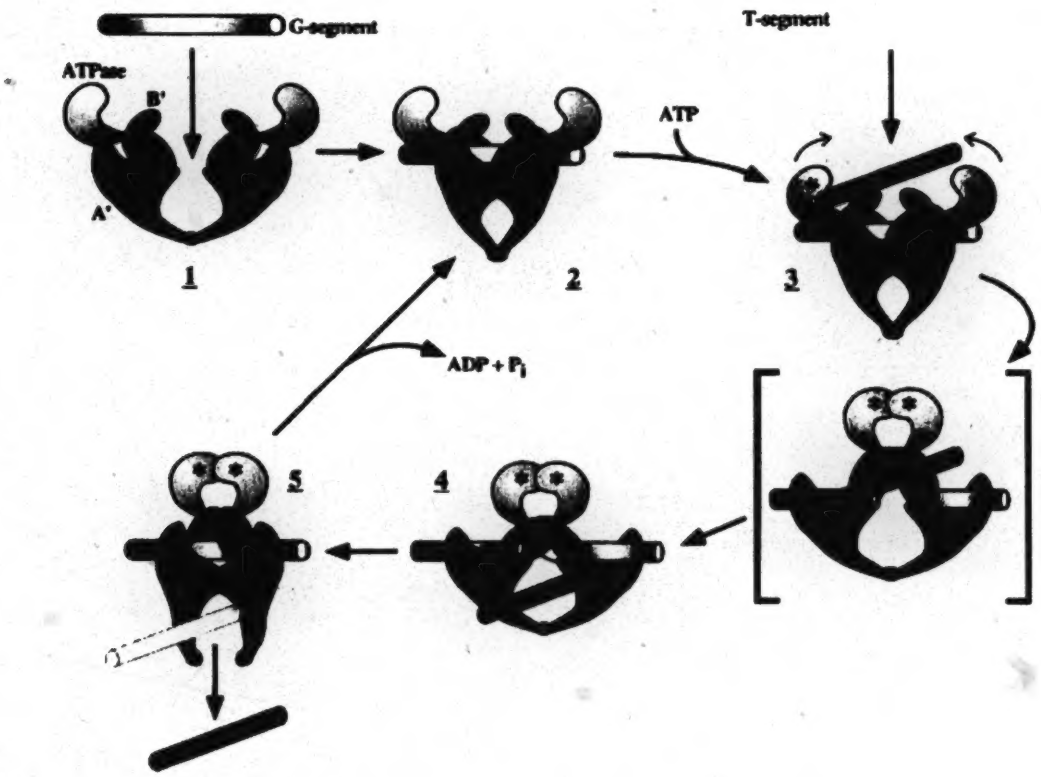
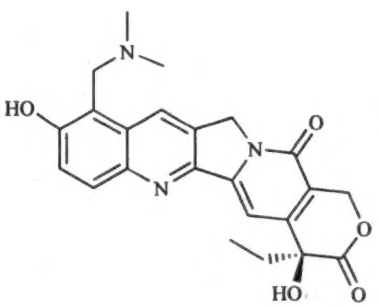


Figure 1.2.3. Schematic Model for Topoisomerase II-mediated DNA Cleavage and Religation. [15] (Adapted from Berger *et. al.*)

1.3. Topoisomearse Inhibitors

Inhibitors of topoisomerase I and II are classified as either poisons or suppressors. Topisomerase poisons act by increasing the DNA cleavage rate or by reducing the DNA religation rate, via the formation of a stabilized cleavable complex intermediate. The stabilization of this complex will ultimately cause DNA damage in the genome leading to apoptosis.[17] The general consensus is that the inhibitory effect arises from the formation of a ternary structure between the drug, the nucleic acid, and the enzyme. An x-ray crystal structure of human topoisomerase I convalently joined to DNA and bound together with the anticancer agent Topotecan **1.2** has recently been reported.[18] Results indicate that in the ternary complex, Topotecan intercalates at the site of DNA cleavage and is stabilized by base-stacking interactions.

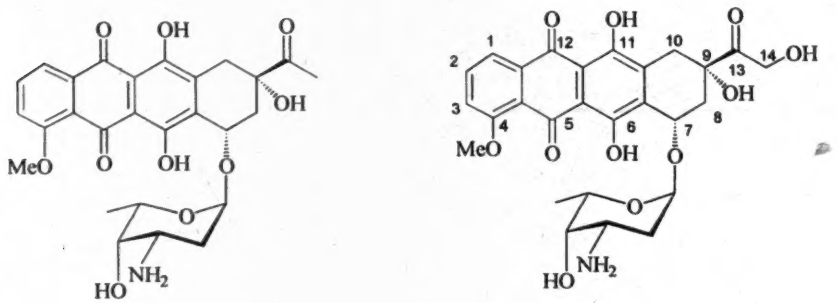


1.2

Figure 1.3.1. Structure of Topotecan.

Topoisomerase suppressors block the activity of the enzyme, therefore preventing DNA cleavage. The majority of the topoisomerase inhibitors that are used for the treatment of cancer act as poisons.[17]

Our main interest is the anthracycline family of antibiotics, which are poisons of topoisomerase I or II. One of the most popular and well studied examples of this antibiotic class is the anticancer agent doxorubicin (Figure 1.3.2.).

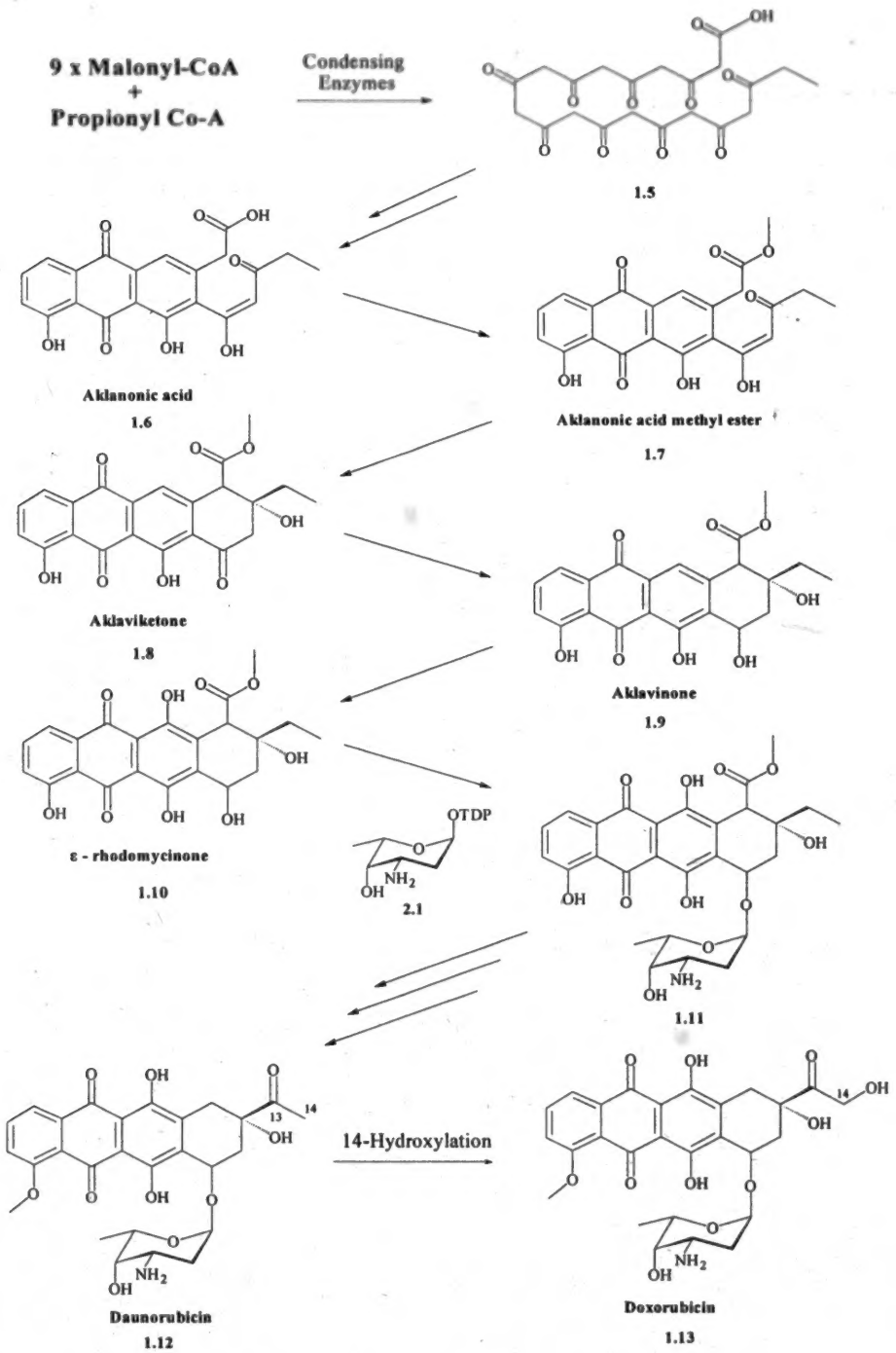


Daunorubicin **Doxorubicin**

1.3 **1.4**

Figure 1.3.2. Structures of Anthracyclines Clinically Used in the Treatment of Cancer.

Daunorubicin **1.3**, isolated from *Streptomyces pencetius*, was first discovered by two independent groups in 1963,[19,20] and was determined to have potent activity against solid tumors.[21,22] Doxorubicin **1.4** was isolated from *Streptomyces peucetius* subsp. *caesius* in 1969,[23] and shows cytotoxic activity against a broader number of tumor cell lines and reduced side effects, as compared to daunorubicin. The two molecules differ only by the replacement of one hydrogen on C-14 in daunorubicin and with an OH group in doxorubicin. These two anthracyclines are deemed important antineoplastic agents because of their effectiveness in treating osteogenic sarcoma and other neoplasias, neuroblastomas, lymphomas, and leukemias.[21]



Scheme 1.3.1. Biosynthetic Pathway from Malonyl-CoA and Propionyl-CoA Precursors to Anthracycline Antibiotics.[25,28]

The biosynthesis of these anthracycline compounds (Scheme 1.3.1.) starts with the precursor aklavinone, which is synthesized from the condensation reaction of nine equivalents of malonyl-CoA and a propionyl-CoA starter molecule.[24] The aglycon common to all anthracyclines is formed from the cyclization of the polyketide chain, followed by a series of reactions that lead to the important intermediate of ε-rhodomycinone.[25] The unglycosylated aglycone is biologically inactive,[26] and therefore, glycosylation is needed to afford an active compound. The glycone of natural anthracyclines is typically daunosamine; however, other types of sugars have also been observed.[27] Glycosylation at the C-7 hydroxyl group with daunosamine followed by subsequent transformations provides daunorubicin. An enzyme, cytochrome P-450 in the DoxA gene of the *Streptomyces* sp. Strain C5 catalyzes the hydroxylation at C-14 to yield doxorubicin.[23, 24]

Even with the popularity of anthracycline compounds used for the treatment of common tumors, much of the molecular basis for its antitumor activity remains unknown.[29] In recent years, researchers have hypothesized possible modes of action for these antibiotics by investigating the interactions between the drug, DNA and protein. It has been well established that anthracycline antibiotics bind to DNA through intercalation of the aromatic portion between adjacent nucleoside base pairs, while the sugar residues and the saturated ring of the anthraquinone reside in the minor groove.[30, 31] The intercalating molecular structure of the anthracycline shows preference for GC base pairs of the DNA, and this trend has been identified from single-crystal x-ray diffraction experiements. (Figure 1.3.3.).[32]

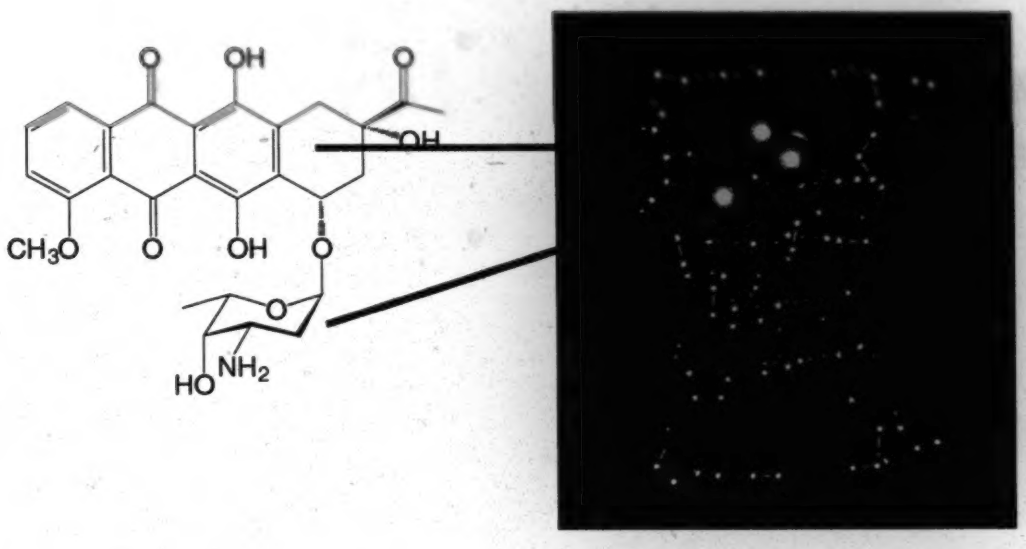


Figure 1.3.3. Crystal Structure of Daunomycin-DNA Complex. The Anthraquinone Moiety Intercalates Between GC Base Pairs, and the Amino Sugar Sits in the Minor Groove.[32]

In an earlier x-ray study, two anthracycline compounds were crystallized together with the DNA sequence d(CGATCG). The DNA-drug complex also revealed a strong preference for intercalating between the C-G base pairs at the ends of the DNA helix. The daunosamine sugar, was shown to occupy the minor groove just outside the intercalating site of the A-T base pair (Figure 1.3.4.).[33]

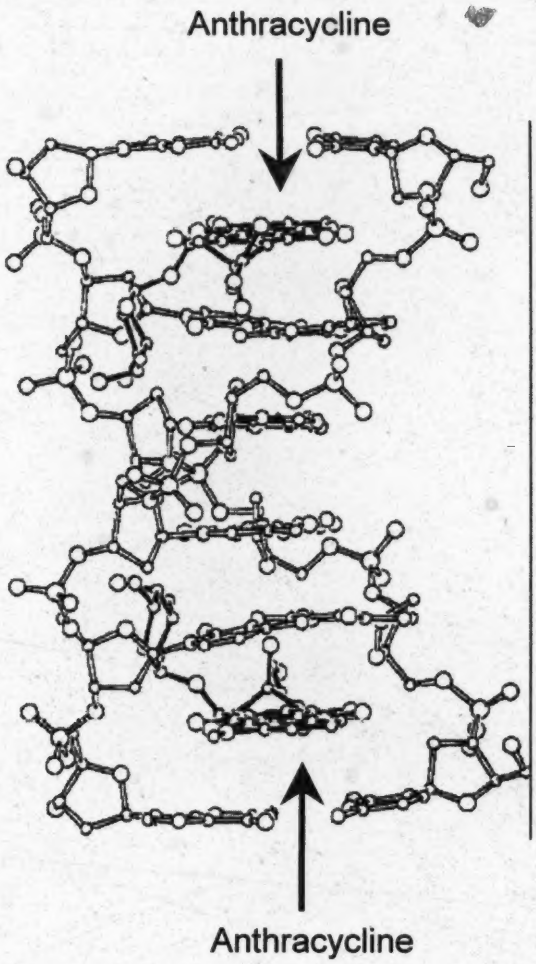


Figure 1.3.4. ORTEP Representation of Two Anthracycline Compounds Bound to d(CGATCG).[33]

Other experimental methods, such as surface-enhanced resonance Raman scattering spectroscopy,[34] spectroelectrochemical methods (i.e. redox reactions),[35] equilibrium measurements between DNA and drug (K_a and K_d) and fluorescence titration,[36] have all been used to elucidate and verify the mode of binding of anthracyclines with DNA.

Computational modelling of 65 doxorubicin analogs and doxorubicin bound to eight DNA octamers has been carried out to determine the free energy of binding and sequence selectivity of these compounds.[37] The results revealed that the replacement of the 4'-OH of daunosamine with a halogen as well as the removal of a methoxy group at the aromatic core of the aglycone portion, led to better selectivity and potency of these compounds toward DNA.[37] This type of experiment is useful in providing a foundation in designing future lead compounds that may possess strong binding affinity to DNA and possibly increasing overall drug potency (Figure 1.3.5.).

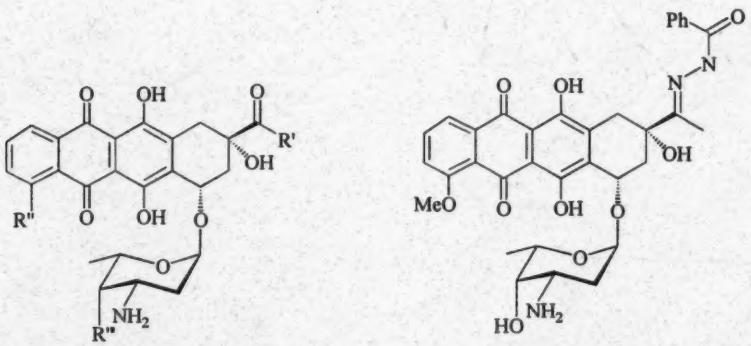


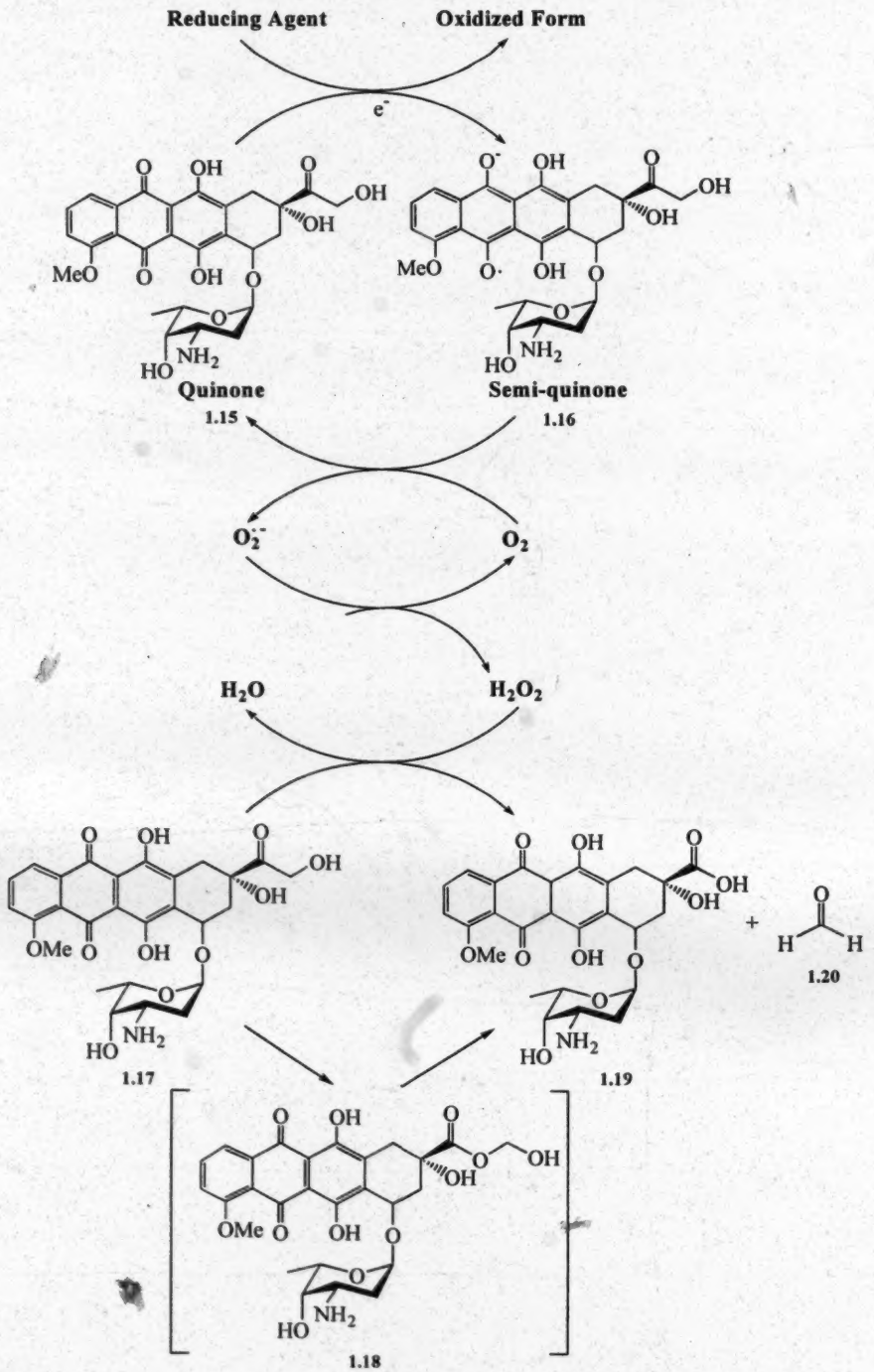
Figure 1.3.5. Structures of Anthracycline Analogs Used in Computational Modelling Study.

Changes in the carbohydrate portion of the anthracycline have also been performed including functional group manipulations, stereochemical changes, and increasing the size of the sugar (e.g. disacharides).[38] The results obtained confirm that the

presence of a second sugar in disaccharide containing anthracyclines and changes to the carbohydrate core does not affect the mode of intercalation of DNA. [39]

1.4. Mechanism of Action and Cytotoxic Effect of Anthracyclines

Having established that doxorubicin and daunorubicin are good DNA binders, researchers have tried to understand the mechanism responsible for their antiproliferative and cytotoxic effects.[40] A number of different mechanisms have been proposed to try to confirm the cytotoxic effect of these agents.[41] Proposed mechanisms of action include the intercalation of the drug into DNA followed by (i) inhibition of macromolecular (eg. DNA and RNA polymerase) biosynthesis,[42, 43] (ii) the formation of free radicals with consequent induction of DNA damage,[44, 45] (iii) lipid peroxidation,[46] (iv) DNA binding and alkylation,[47] (v) DNA cross-linking,[48] (vi) interference with DNA unwinding or DNA strand separation and helicase activity,[49] (vii) and the initiation of DNA damage via inhibition of topoisomerase II.[29, 50] Ultimately, all of the above processes will lead to apoptotic cell death.[51,52,53]



Scheme 1.4.1. Cascade Reactions in DNA-drug Adduct Formation.[58, 59]

The formation of free radicals is quite prominent in both anthracyclines' mode of action and cytotoxic effect to healthy tissue. Free radicals induce DNA damage via a mechanism where the quinone moiety of the anthracycline acts as electron acceptors in reactions mediated by enzymes such as cytochrome P450 reductase and NADH dehydrogenase.[54, 55] The presence of an electron converts the quinone to semiquinone free radicals, which then leads to DNA damage.[56] It is established that the quinone functionality can also serve to catalyze the production of reactive oxygen species in the presence of a reducing agent and molecular oxygen. It is proposed that the presence of these oxygen species leads to tumor cell cytotoxicity and cardiotoxicity.[57]

A recent study suggested that doxorubicin is involved in a complex redox pathway that leads to DNA alkylation (Scheme 1.4.1.).[58] The cytotoxic activity is proposed to arise from a set of cascade reactions beginning with drug reduction, and catalytic production of reactive oxygen species, followed by oxidative synthesis of formaldehyde. This reductive activation of the anthracycline yields hydrogen peroxide, which will lead to a Baeyer-Villiger reaction of the ketone to provide a carboxylic acid **1.19** derivative of the anthracycline, along with formaldehyde.[58]

A recent report also demonstrated that the presence of formaldehyde is essential in the activation of anthracyclines to form DNA adducts *in vitro*, and this has also been demonstrated for tumor cells in culture.[58,59,60]Interestingly, elevated levels of formaldehyde have been detected in cancerous cells, suggesting the possibility that cancer cells supply the formaldehyde needed for further adduct formation and thereby increasing overall toxicity.[61] The generation of the DNA-drug adduct is via the formation

of a Schiff base intermediate that links the 3'-amino group of the anthracycline to the 2-amino group of deoxyguanosine (Figure 1.4.1.).[59]

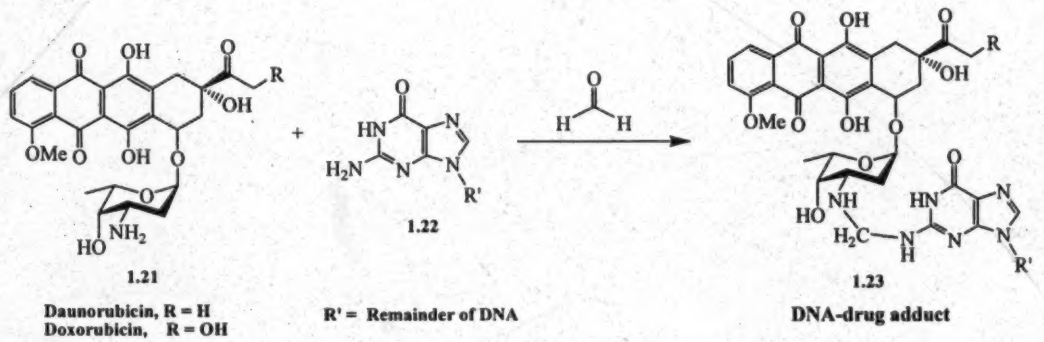


Figure 1.4.1. Formation of DNA-drug Adduct Mediated by Formaldehyde.[62]

In a recent review,[62] the formation of doxorubicin/daunorubicin-DNA adduct by a aminal (N-C-N) linkage has been confirmed with the use of 2D NMR, mass spectrometry and X-ray crystallography. As shown in (Figure 1.4.2.), hydrogen bonding (a) between the drug and the second strand of DNA provides extra stability to the adduct (Figure 1.4.2.).[63]

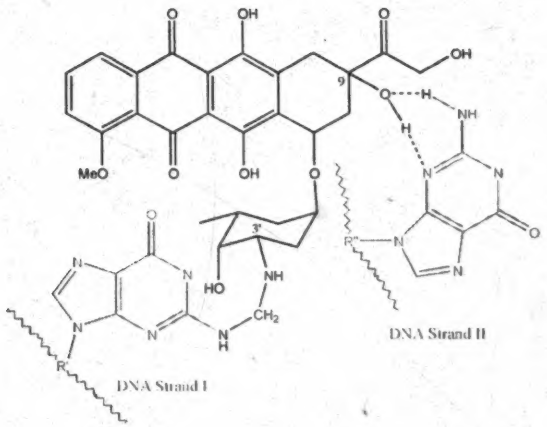


Figure 1.4.2. Structure of Anthracycline-DNA Adduct via Aminal (N-C-N) Linkage. (A) Doxorubicin-DNA Adduct and Stabilization by Second DNA Strand through Confirmation of 2D NMR Study.[62]

The induction of strand breaks in DNA by anthracyclines is evident through the discovery that topoisomerase II is a primary target of doxorubicin.[29, 50] This result was confirmed when tumor cells with reduced levels of the active enzyme were exposed to the drug, a reduction in the level of drug-associated strand breaks in DNA was observed.[64] Anthracycline antibiotics will induce apoptosis, and evidence of this outcome is observed in the treatment of HeLa cells with doxorubicin, which led to cell shrinkage.[51]

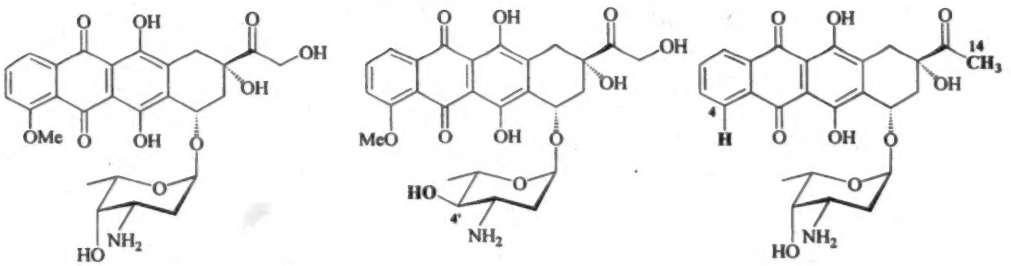
Variation in the type of anthracycline used in conventional treatment can have different *in vitro* cytotoxic activity to certain types of tumor cells.[65] Doxorubicin and daunorubicin are structurally different, and doxorubicin is effective in the treatment of breast cancer, childhood solid tumors, sarcomas and lymphomas, while daunorubicin is active against acute lymphoblastic leukemia and aggressive lymphomas.[66,67] Even though the anthracyclines currently in use are effective in combating tumor cells, the toxic side

effects associated with these drugs remain problematic. Doxorubicin and daunorubicin have both been shown to lead to the development of chronic cardiomyopathy and congestive heart failure when used long term.[68] Anthracyclines induce cardiotoxicity via activation of a series of complex pathways that lead to apoptosis of cardiomyocytes (muscle cells of the heart).[67,69] This apoptotic action is different to that of the normal pathway that mediates anthracyclines' antitumor effect against cancer cells, and researchers have suggested that cardiomyocytes may be more susceptible than other tissues to apoptosis upon exposure to doxorubicin. Certain *in vitro* studies have shown that doxorubicin will induce apoptosis by favoring the release of the enzyme cytochrome *c*, which will lead to the activation of apoptosis factors within the cell. At higher drug concentrations, the 7-deoxy-aglycone of doxorubicin can accumulate inside the mitochondrial membrane thus leading to the formation of oxygen radicals and hydrogen peroxide that causes mitochondrial failure. The 7-deoxy-aglycone of doxorubicin was observed to be more potent than doxorubicin itself and can permeate the inner mitochondrial membrane more easily. Methods have been developed to reduce cardiotoxicity, such as the slow infusion of the drug over a period 2-3 days, and results have shown that there is a slight reduction in cardiotoxicity while retaining drug effectiveness.[70] The use of antioxidants had also been examined, but there was no clear cut result as to which type of antioxidant was better.[71] The effectivness of these methods is questionable, and there is no specific treatment for doxorubicin-related cardiotoxicity. Currently, researchers have not been able to devise specific methods to differentiate between selective protection of the heart against damages induced by anthracyclines. Because there is no specific treatment for anthracycline-related cardiotoxicity, the

development of new analogs that can achieve good therapeutic response and minimize cardiac toxicity is of interest. Therefore, the focus of my research was to develop novel inhibitors that could potentially serve to bind to DNA and inhibit topoisomerase activity, in turn killing cells.

1.5. Novel Anthracyclines

The mechanism of cytotoxic action associated with anthracyclines involves intercalation into DNA and topoisomerase II-mediated strand breaks. Moreover, doxorubicin and daunorubicin target topoisomerase II and have little effect on topoisomerase I. The inhibition associated with the enzyme topoisomerase I, if any, does not involve the trapping of the covalent DNA-topoisomerase I cleavable complex, therefore, suggesting that inhibition is nonspecific. Rather, inhibition of DNA-processing enzymes associated with DNA bound to topoisomerase I may be the case.[72] In recent years, medicinal chemists have developed a number of new anthracyclines analogs. Structural changes and functional group modifications of traditional antibiotics, like doxorubicin and daunorubicin, have yielded an array of compounds with better antitumor activity and reduced toxicity. For example, modifications to either the aglycone or the monosaccharide portion have led to the second generation of anthracycline analogs: epirubicin and idarubicin (Figure 1.5.1.). These compounds serve as an alternative to doxorubicin and daunorubicin and have been approved and used in the clinical treatment of doxorubicin-resistant tumors.



Doxorubicin
1.24

Epirubicin
1.25

Idarubicin
1.26

Figure 1.5.1. Structures of Doxorubicin, Epirubicin, and Idarubicin.

Epirubicin **1.25** is the C-4' hydroxyl epimer of the daunosamine moiety of doxorubicin. This slight change has little effect on the mode of action and activity of epirubicin, but the pharmacological changes associated with epirubicin use reveal better activity towards topoisomerase II and a decrease in overall cardiotoxicity.[72]

Idarubicin **1.26** is an analog of daunorubicin with the 4-methoxy group of the aglycone removed. Idarubicin is effective in the treatment of leukemia, myeloma, lymphoma and breast cancer, and this result is attributed to its ability to form a stabilized ternary-drug-topoisomerase II-DNA complex via an increase in lipophilicity and cellular uptake.[40, 73]

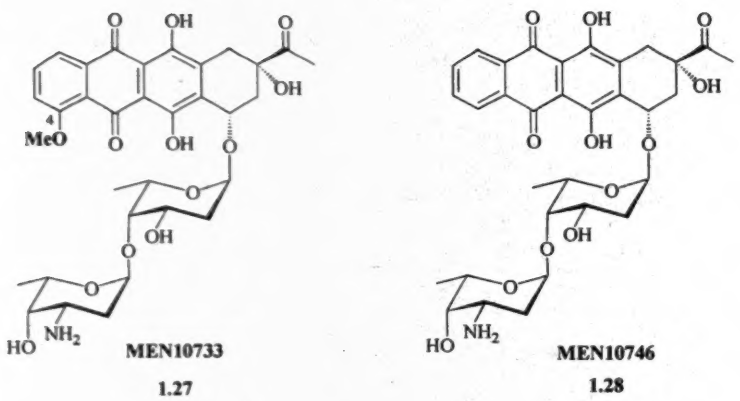
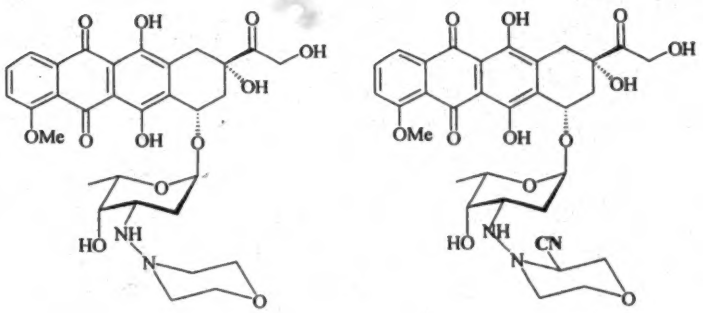


Figure 1.5.2. Structure of Idarubicin Dissacharide Analogs[74]

It has also been reported that idarubicin analogs bearing a disacharide moiety in which both sugar residues have α-linkages e.g., MEN10733 **1.27**, which has a C-4 methoxy group, and MEN10746 **1.28** (Figure 1.5.2.) stimulated topoisomerase I-dependent DNA cleavage. These idarubicin analogs were tested for topoisomerase I DNA cleavage ability and compared with the topoisomerase I specific drug, camptothecin. However, none of these disacharide analogs were as active and as potent as camptothecin. The cytotoxic activities of these disacharide anthracyclines are not as effective towards topoisomerase I as compared to topoisomerase II, but these compounds could still be considered dual poisons of both type I and II topoisomerases. It may be the case that these compounds, which are thought to be specific for topoisomerase II, might also be targeting topoisomerase I.[74]



MRA
1.29

MRA-CN
1.30

Figure 1.5.3. Structures of Morpholinyl and Cyanomorpholinyldoxorubicin.[75]

Morpholinodoxorubicin **1.29** and cyanomorpholinyldoxorubicin **1.30** (Figure 1.5.3.) are topoisomerase I inhibitors. These two compounds were shown to be able to suppress enzyme-mediated DNA cleavage induced by topoisomerase I. Structurally, these two compounds are similar to doxorubicin, and target topoisomerase II, but with the addition of a morpholinyl group, these new analogs become topoisomerase I inhibitors.[75] This outcome suggests that by adjusting the structural features of an inhibitor that target topoisomerase II, these compounds may also target topoisomerase I.

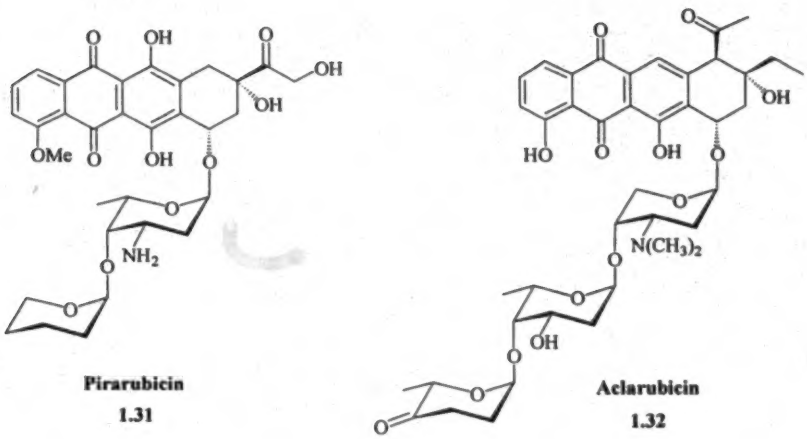


Figure 1.5.4. Structures of Pirarubicin and Aclarubicin.

Other anthracyclines that have gained clinical approval in recent years include pirarubicin **1.31** and aclarubicin **1.32** (Figure 1.5.4.). Pirarubicin, a 4-tetrahydropyranyl derivative of doxorubicin shows better activity and less cardiotoxicity than doxorubicin in animal models and shows inhibitory activity towards topoisomerase II.[74] Aclarubicin, a trisaccharide anthracycline, can stabilize DNA-topoisomerase I covalent complex and inhibits DNA-protein cross-linking in tumor cells. Aclarubicin is a dual topisomerase I and II poison; NMR studies have shown that the interaction between the trisaccharide moiety of the drug and DNA leads to the formation of a kink in the DNA double helix. This kinking of the DNA is not observed with either doxorubicin or daunomycin, and this may be the reason behind aclarubicin's inhibitory effect on both toposiomerase I and II.[75]

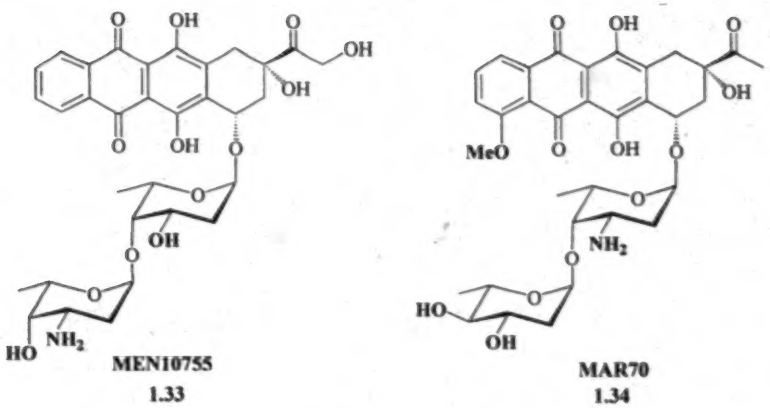
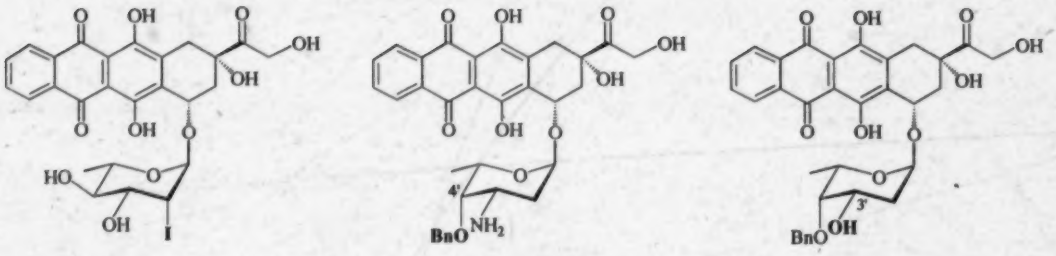


Figure 1.5.5. Structures of MEN10755 and MAR70.

Other disaccharide containing analogs, MEN10755 **1.33** and MAR70 **1.34** (Figure 1.5.5.), are both compounds that differ in the amino sugar sequence of their disaccharide chains and stereochemistry of dihydroxy sugar. These compounds bind DNA differently based on the interaction of their amino sugar with the DNA strand.[39] Researchers predict that the enhanced ability of these compounds to inhibit both topoisomerase I and II may be the result of this second sugar moiety,[38] and efforts are being made to prepare analogs of these anthracycline disacharides in order to prove this hypothesis. This result suggests that modification of the anthracycline (e.g., extending the sugar chain) and observing its interaction with DNA can lead to the design of inhibitors that could target either or both topoisomerase I and II.



Annamycin
1.35

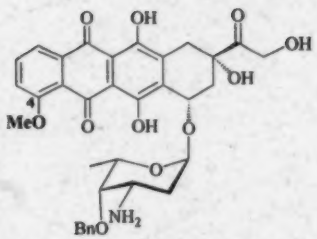
WP769
1.36

WP794
1.37

Figure 1.5.6. Annamycin and 4-Demethoxy Analogs of Anthracyclines.[76]

In a recent study by Priebe and co-workers, they were able to show that 4-demethoxy analogs of doxorubicin exhibited enhanced ability to target topoisomerase II. The compound, annamycin **1.35**, which contains an iodine group at C-2', WP769 **1.36** and WP794 **1.37** (Figure 1.5.6.), showed greater ability to trap the topoisomerase II cleavable complex. These 4-demethoxy analogs showed better induction towards DNA-protein crosslinks, a process that leads to DNA strand breaks, as compared to doxorubicin.[76]

The same group that had synthesized the 4-demethoxy analog WP769 had also prepared the 4-methoxy analog WP744 (Figure 1.5.7.). Their results showed that the anthracycline WP744 **1.38** could cross the blood-brain barrier and able to inhibit topoisomerase II. Currently, this compound is being used in phase I clinical trial in the treatment of advanced brain cancer.[77]



WP744

1.38

Figure 1.5.7. Structure of WP744.[77]

Wang and co-workers also prepared a number of disaccharide daunorubicin analogs (Figure 1.5.8.) that showed better anticancer activity along with improved inhibition towards topoisomerase II. Their results verified that the attachment of a second 2,6-dideoxy sugar residue that possesses an α-linkage to the first sugar was critical in enhancing anticancer activity.[38]

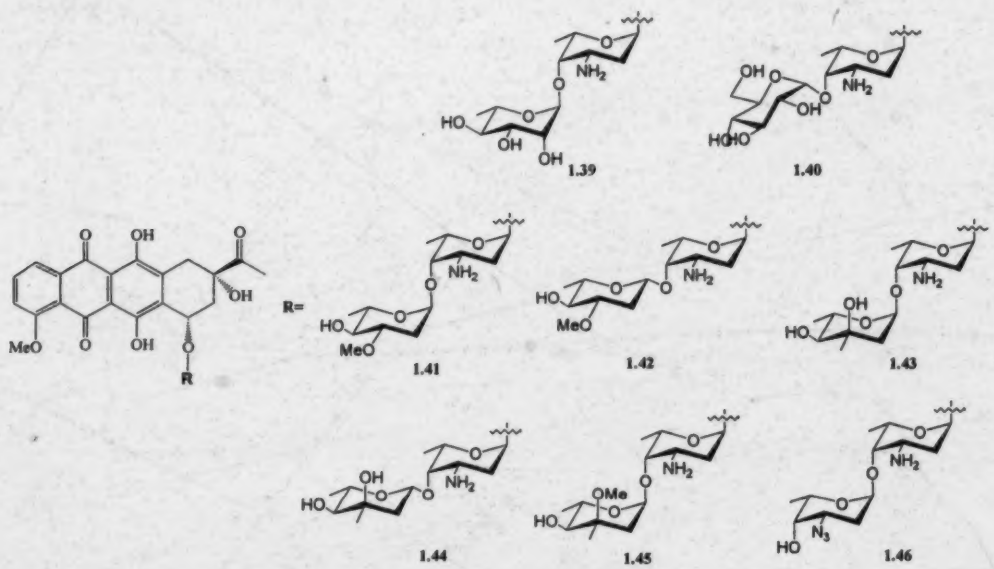
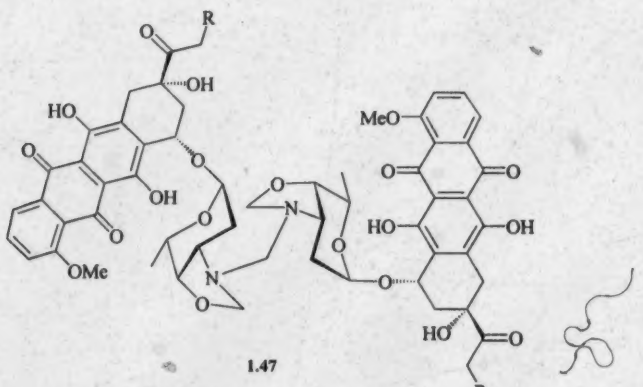


Figure 1.5.8. Disaccharide Daunorubicin Analogs Synthesized by Wong and Co-workers.[38]

Pre-activated anthracyclines make up another class of compounds that have received greater attention in recent years. As mentioned previously (Section 1.4), DNA can form aminal-linked adducts in the presence of formaldehyde via Schiff base intermediates. Pre-activated anthracyclines utilize the same principle as the formation of DNA-drug adducts. However, two anthracyclines are joined together by a methylene bridge; these dimeric anthracyclines **1.47** are referred to as Doxoform and Daunoform (Figure 1.5.9.).[78] Hydrolyses of these dimers liberates the active drug and formaldehyde, thus allowing DNA-drug adducts to be formed. It has been reported that pre-activated drugs can form adducts with DNA much faster than the drug alone in the presence of formaldehyde. Doxoform was shown to be 150-fold more active against MCF-7 human breast cancer cells and 10,000-fold more active against MCF-7/ADR cells compared to doxorubicin. These exceptional results may be due to faster and greater nuclear uptake of these pre-activated anthracyclines.[78,79]



1.47

R = H, Daunoform
R = OH, Doxoform

Figure 1.5.9. Structure of Doxoform and Daunoform.[78]

1.6. Research Overview

Even though numerous DNA toposiomerase inhibitors have been developed over the last 40 years, the preparation of novel inhibitors with reduced toxicity remains an important area of research. The compounds described in this thesis are inspired by the structure of the anthracycline antibiotics. Our approach was to synthesize analogs (Figure 1.6.1.) of these compounds that possess a simpler intercalating core while linked to the traditional daunosamine moiety, as well as other amino sugars. In Chapter 2, the synthesis of these compounds and their subsequent screening for cytotoxic activitiy towards cancer cell lines will be discussed.

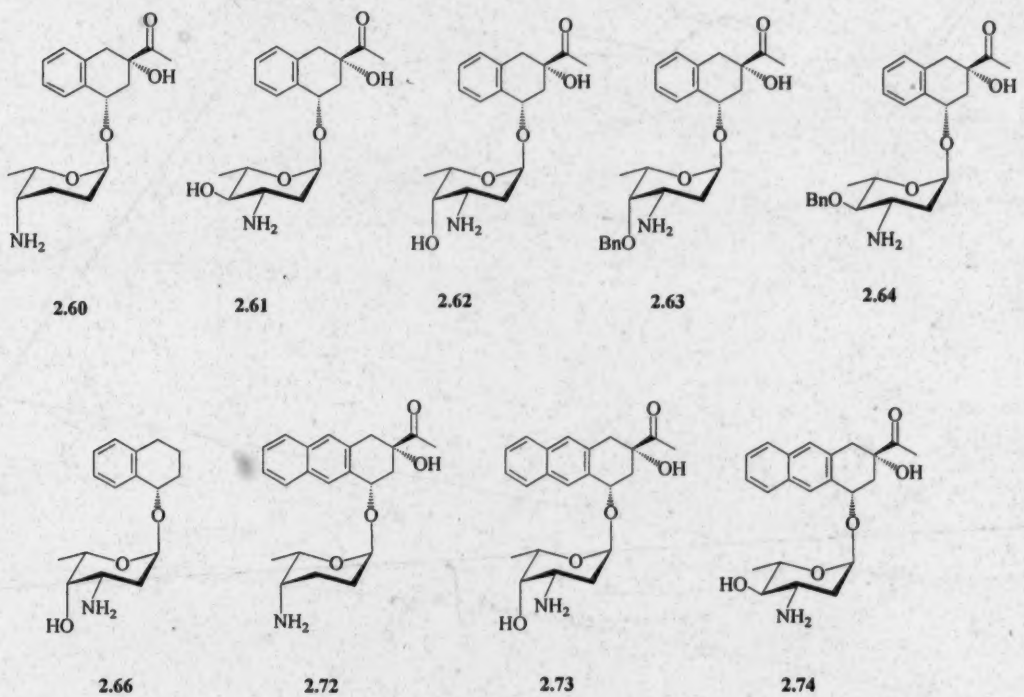


Figure 1.6.1. Structure of Anthracycline Analogs that were Synthesized.

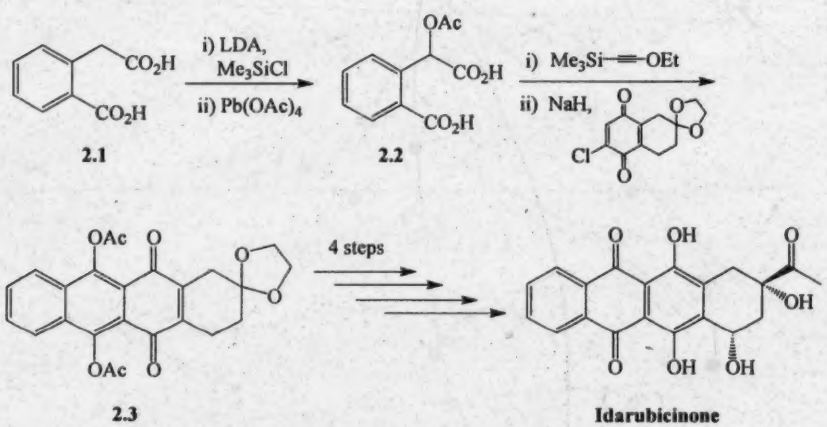
CHAPTER 2

PREPARATION OF ANTHRACYCLINE MIMETICS. SYNTHESIS OF 1,2,3,4-TETRAHYDRO-NAPHTHYL/ANTHRANYL CORES AND THIOGLYCOSIDE DONOR AND THEIR GLYCOSYLATION REACTIONS.

2.1. Background

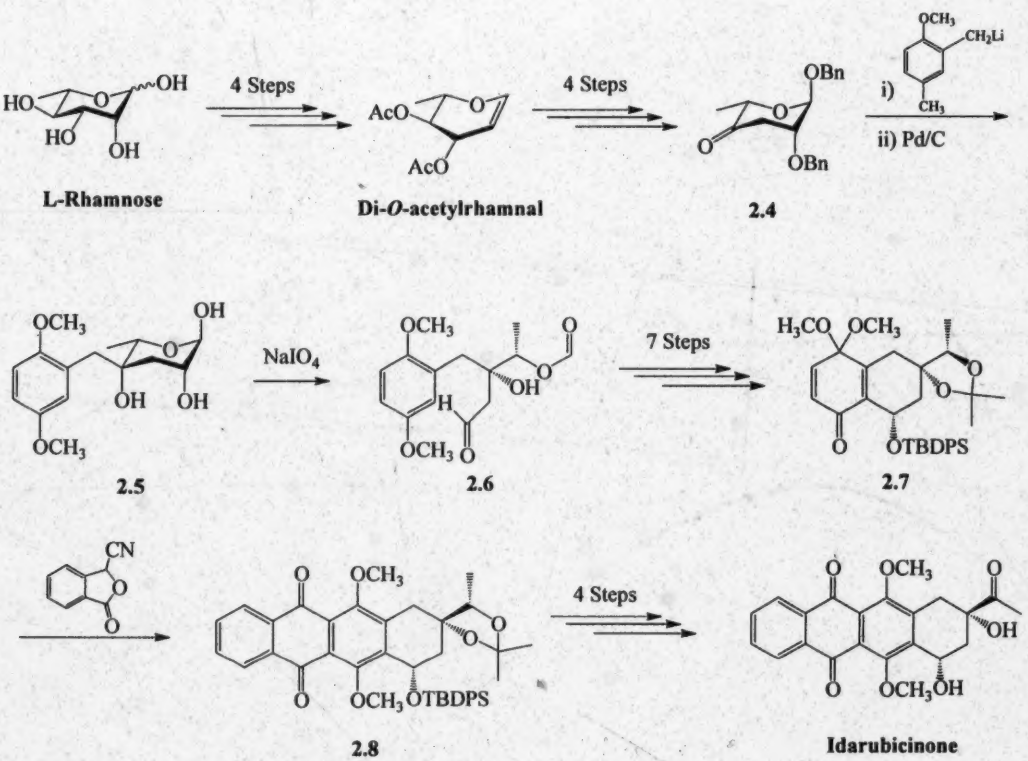
Anthracyclines are effective stabilizing agents of the topoisomerase-DNA complex via intercalation of the aromatic moiety and binding of the carbohydrate moiety in the minor groove. However, the chemical synthesis these compounds tend to be lengthy and tedious, and in particular, accessing the anthraquinone moiety requires lengthy synthetic routes.

In recent years, methods have been devised to prepare these complex target molecules. As an example,[80] one method involves the use of homophthalic acid **2.1** with trimethylsilyl chloride followed by oxidation with lead tetraacetate to form 2-acetoxylated homophthalic acid **2.2**. Treatment of this acid with trimethylsilylethoxyacetylene followed by reaction with 2-chloro-6-oxo-5,6,7,8-tetra-
hydro-1,4-naphthoquinone 1,2-ethanediyl acetal in the presence of sodium hydride leads to the tetracyclic core **2.3**. Further manipulations of this core will lead to the target anthracycline compound (Scheme 2.1.1.).



Scheme 2.1.1. Synthesis of Idarubicinone Using Homophthalic Acid.[80]

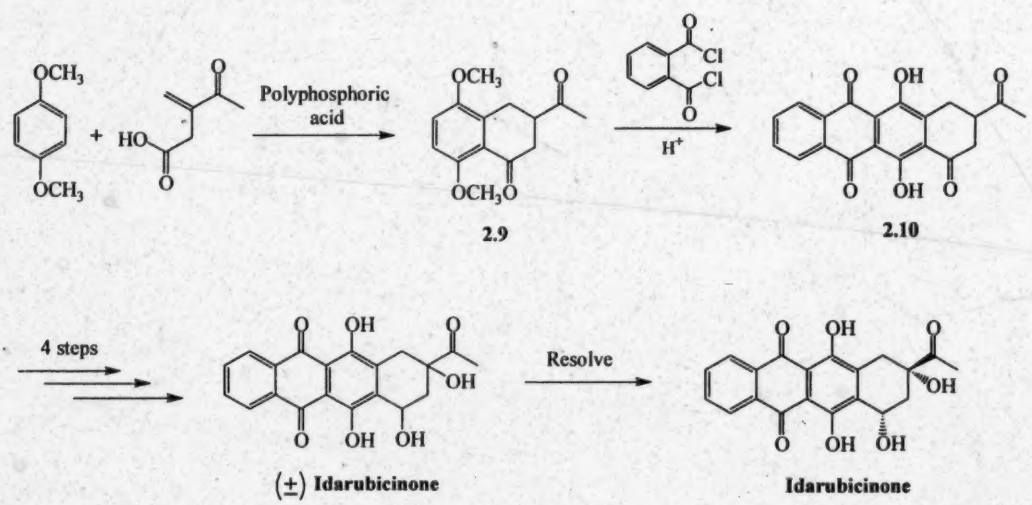
The use of L-rhamnose as a chiral starting material leading to the target idarubicinone has also been examined (Scheme 2.1.2.).[81] Ketone **2.4** could be prepared via the corresponding 3,4-di-*O*-acetyl-rhamnal in four steps, and this product could be further transformed into pyranose **2.5** upon treatment with 2,5-dimethoxybenzylithium. Periodate cleavage of this compound afforded the dihydroxyaldehyde **2.6**, which is a precursor of the AB fragment of the target anthracycline. Further transformation of compound **2.6** through a seven-step reaction sequence led to the ketoacetal **2.7**. Annulation of 3-cyano-1(3*H*)-isobenzofuranone to the ketoacetal gave rise to the tetracyclic compound **2.8**, and further modifications then led to the target idarubicinone.



Scheme 2.1.2. Synthesis of Idarubicinone from L-Rhamnose.[81]

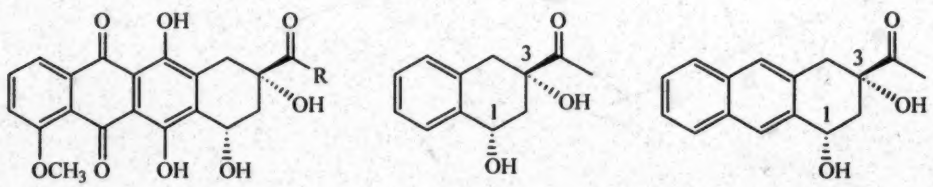
Another method (Scheme 2.1.3.) involved the formation of the A and B ring system of the anthracycline by reaction of 1,4-dimethoxybenzene **2.9** with a β,γ-unsaturated carboxylic acid derivative in the presence of polyphosphoric acid. Formation of the C and D ring in the presence of phthaloyl chloride, led to compound **2.10**. This compound was further transformed into the corresponding racemic form of the target idarubicinone, and this mixture was resolved by attaching a chiral auxiliary to its secondary alcohol followed by removal of the auxiliary to afford the pure enantionmer of the target.[82]

Even though numerous papers have been published over the years describing the preparation of these anthracycline compounds, the long synthetic sequence associated with these methods coupled with their low yield and by-product formation, limit the feasibility of making analogs of these structures.



Scheme 2.1.3. Synthesis of Idarubicinone from Carboxylic Acid Derivatives.[82]

My research involves the syntheses of two simplified anthracycline analogs that would potentially intercalate into DNA and inhibit topoisomerases, and thus be cytotoxic. We chose the 1,2,3,4-tetrahydro-naphthyl **2.11** and 1,2,3,4-tetrahydro-anthranyl **2.12** cores to be the aglycone of our targets due to the structural simplicity compared to the complex quinone moiety of the anthracycline compounds (Figure 2.1.1.). Realizing that the anthraquinone moiety of anthracyclines intercalates into DNA, we proposed that a simplified version of the aglycone core could behave in the same manner. The two stereogenic centers of the saturated ring were chosen to be identical to that of the anthracyclines, as the stereochemistry of these centers is critical for interaction with the DNA.[32]



R = H, CH_2OH
Anthracycline Aglycone

1,2,3,4-Tetrahydro-naphthyl

2.11

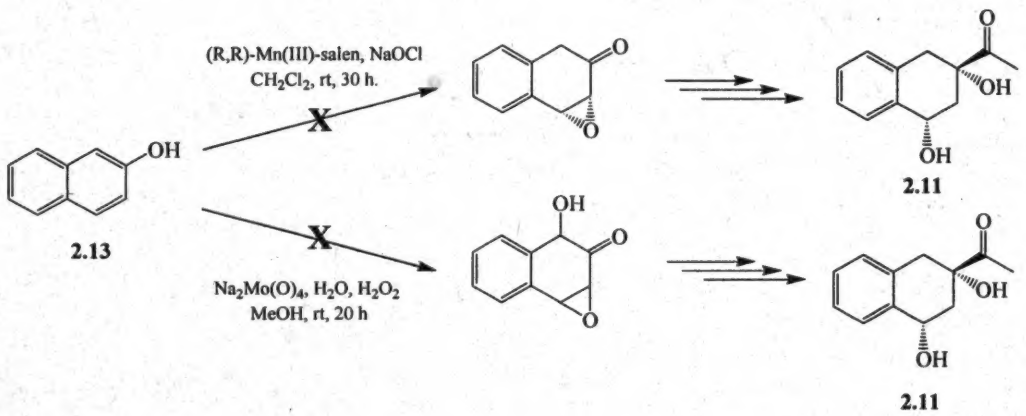
1,2,3,4-Tetrahydro-anthranyl

2.12

Figure 2.1.1. Structures of the 1,2,3,4-Tetrahydro-naphthyl **2.11** and 1,2,3,4-Tetrahydro-anthranyl **2.12** Aglycone Cores.

2.2. Synthesis of the 1,2,3,4-Tetrahydro-naphthyl Core

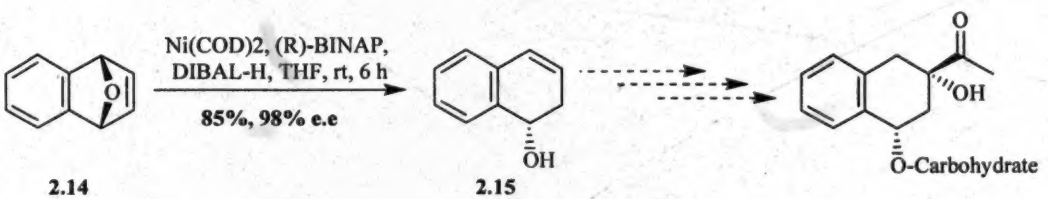
Initially we attempted to access the 1,2,3,4-tetrahydro-naphthyl core from the readily available 2-naphthol **2.13** by epoxidation with Jacobsen's catalyst (*R,R*)-Mn(III)-salen and NaOCl.[83] Unfortunately, no product was obtained. We next focused our attention to a method developed by Barton and co-workers[84] in which 2-naphthol could be converted into the racemic α-hydroxy-δ-epoxy ketone by treatment with sodium molybdate and H_2O_2. Once again, no product was obtained (Scheme 2.2.1.).



Scheme 2.2.1. Synthesis of the 1,2,3,4-Tetrahydro-naphthyl Core Using Jacobsen's Catalyst and Sodium Molybdate.

Faced with these difficulties, we explored a route that as a key step, involved the formation of the enantiomerically pure (*S*)-(1H,2H)-dihydronaphthalen-1-ol **2.15** in 85% yield and 98% e.e. from oxabicyclic alkene **2.14** using a method developed by Lautens and co-workers (Scheme 2.2.2.).[85] This important intermediate provides an alcohol with the

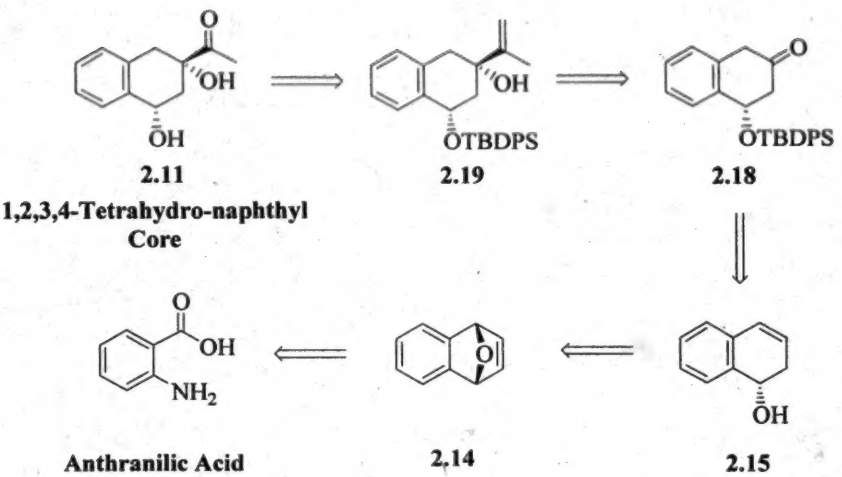
desired stereochemisty at C-1, at which glycosylation will take place at a later stage. Having established that this very useful precursor could potentially lead us towards our target 1,2,3,4-tetrahydro-naphthyl core, we therefore decided to employ this strategy.



2.14 **2.15**

Scheme 2.2.2. Preparation of 1,2,3,4-Tetrahydro-naphthyl Target from (*S*)-(1H,2H)-dihydronaphthalen-1-ol.

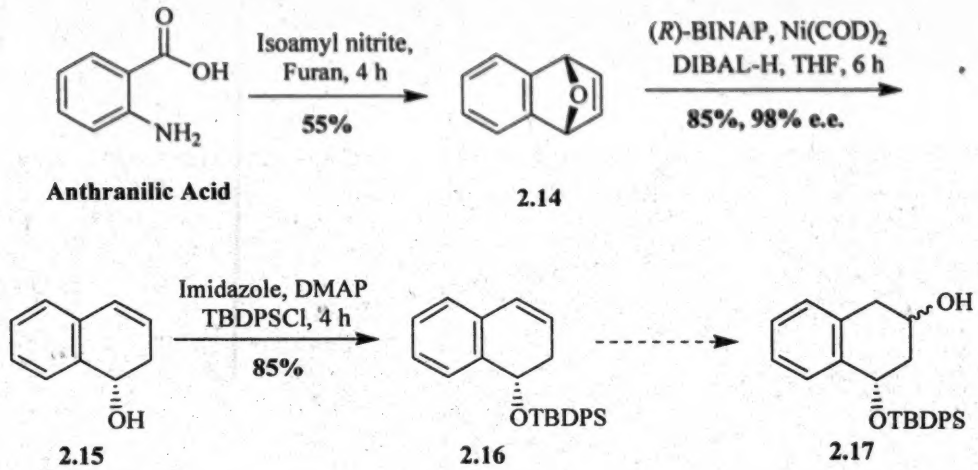
In the retrosynthesis (Scheme 2.2.3.), the naphthyl core **2.11** could be acquired via ozonolysis of alcohol **2.19** followed by removal of the protecting group. This alcohol would arise from the corresponding ketone **2.18** via an addition reaction to the carbonyl by a carbon nucleophile. The steric influence of the protecting group at the O-1 position should allow for attack of the incoming nucleophile at the carbonyl center from the top face of the ring therefore leading to the desired stereochemistry. Ketone **2.18** could arise from the secondary alcohol precursor **2.15** via the nickel catalyzed asymmetric reductive ring opening of the oxabicyclic alkene[85] **2.14** and this alkene could be prepared from commerically available anthranilic acid.



Scheme 2.2.3. Retrosynthesis of 1,2,3,4-Tetrahydro-naphthyl Core.

To explore the feasibility of this approach (Scheme 2.2.4.), oxabenzonorbornene **2.14** was prepared with an overall yield of 55% by generation of benzyne from anthranillic acid and isomayl nitrite followed by in situ trapping with furan.[86, 87, 88] This bicyclic olefin was then subjected to the nickel catalyzed asymmetric reductive ring-opening reaction in the presence of (*R*)-BINAP and DIBAL-H to yield alcohol **2.15** with an overall yield of 85%.[85, 89] The e.e. of this intermediate was 98% as verified by chiral HPLC, and the optical rotation obtained was $[\alpha]_D$ -35.8 as compared to that of the literature value[85] of $[\alpha]_D$ -41.1. The same sign of these rotations enabled us to determine that we had the correct stereochemistry at C-1.

The secondary alcohol was subsequently protected as the TBDPS ether to provide compound **2.16** with an overall yield of 85%.[85]



Scheme 2.2.4. Preparation of Secondary Alcohol **2.17**.

Various methods were examined to generate secondary alcohol **2.17** (Table 2.2.1.). These included (a) hydroboration with BH_3 followed by oxidation with H_2O_2,[90] (b) hydroboration with 9-BBN followed by oxidation,[90] (c) epoxidation using *m*CPBA followed by hydride ring opening with $LiAlH_4$,[91] (d) epoxidation with *m*CPBA followed by hydride ring opening with BH_3/Et_3SiH,[92] and (e) epoxidation with DMDO,[93] followed by ring opening with $LiAlH_4$. The hydroboration methods employed provided none of the desired product. However, epoxidation[90] with *m*CPBA followed by ring opening with $LiAlH_4$ afforded the desired product **2.17** in only 30% yield over the two steps. As well, epoxidation [91] with *m*CPBA followed by opening of the epoxide with BH_3 and Et_3SiH afforded no product. With the use of DMDO followed by hydride ring opening, the yield of the product was increased. We speculated that under the acidic condition of *m*CPBA oxidation that elimination of the secondary alcohol and loss of the -OTBDPS group may occur therefore leading to the formation of naphthalene. By using DMDO as the oxidant,

the reaction proceeds under neutral condition and the formation of this by-product could be avoided. This reaction sequence gave an overall yield of 80% over two steps. The regioselective control in the opening of the epoxide could be explained via the formation of a benzylic cation like intermediate that favors the attack of the hydride at the benzylic position, and this result has also been previsouly documented on similar types of system.[90] Hydroboration using BH_3 followed by oxidation using TPAP and NMO[94] to generate ketone **2.18** directly was also examined, but this was unsuccessful.

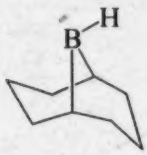
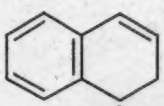
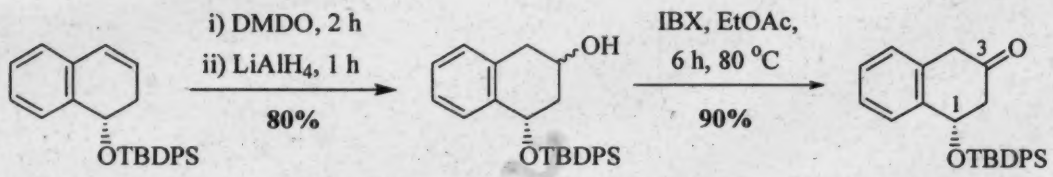
Starting Material	Conditions	Yield
	i) $BH_3 \cdot THF$ ii) H_2O_2	0%
	i)  ii) NaOH, H_2O_2	0%
 OTBDPS **2.16**	i) *m*CPBA ii) $LiAlH_4$	30%
	i) *m*CPBA ii) BH_3, Et_3SiH	0%
	i) ii) $LiAlH_4$	**80%**
	i) $BH_3 \cdot Me_2S$ ii) TPAP/NMO	0% (Ketone)

Table 2.2.1. Conditions Examined for the Preparation of Alcohol **2.17**.

Alcohol **2.17** was oxidized using IBX in ethyl acetate[95,96] to yield the corresponding ketone **2.18** in 90% (Scheme 2.2.5.). This mild method seems to be a good choice because purification by chromatography was needed to isolate the product, and therefore other oxidation methods were not examined.

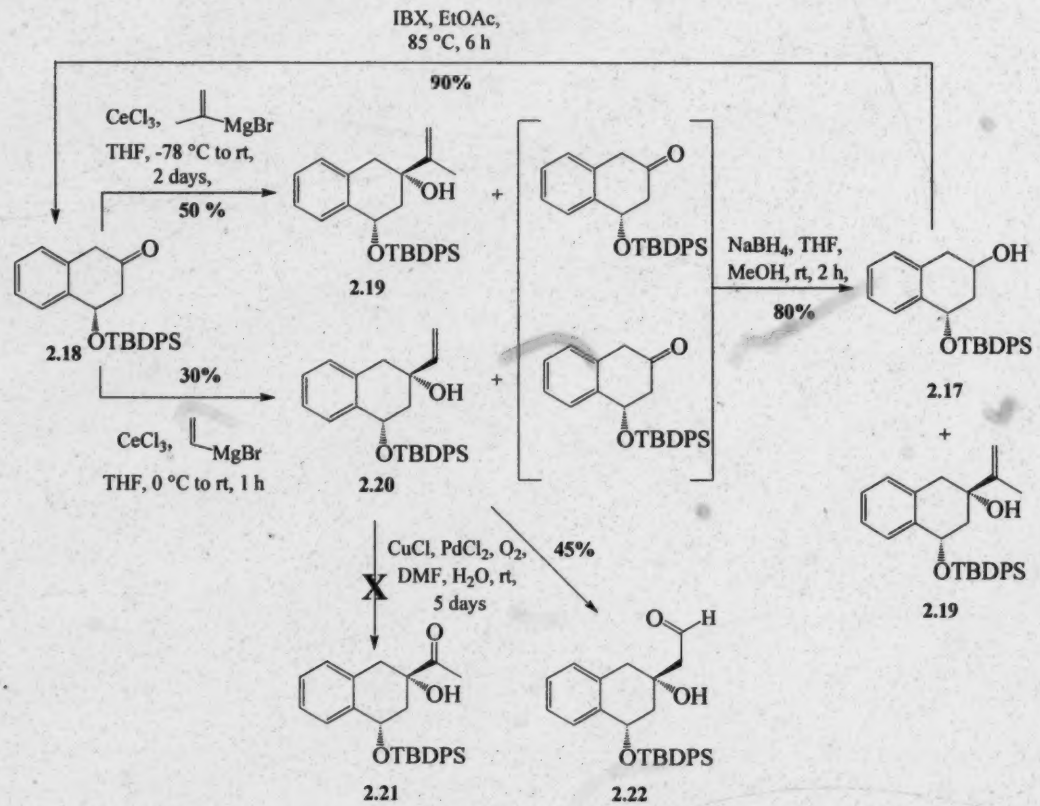


2.16 **2.17** **2.18**

Scheme 2.2.5. Preparation of Ketone **2.18**.

With the ketone in hand, an addition reaction using a Grignard reagent would allow us to install a new stereogenic center at C-3 (Scheme 2.2.6.). The addition reaction using isopropenyl magnesium bromide alone afforded no product and only starting material remained. We believed that the strong basicity of the Grignard reagent led to enolate formation, thus preventing addition to the ketone. The use of an organolithium reagent generated from *t*-BuLi and 2-bromopropene[97] also did not lead to any desired product. The addition of a $CeCl_3$ reagent along with isopropenylmagnesium bromide led to the desired product with only 50 % conversion and recovery of starting material.[98] We also attempted to use a vinylmagnesium bromide reagent[99] in the presence of $CeCl_3$ to afford the vinylic product **2.20**. Having isolated this intermediate, a Wacker oxidation

reaction[100] could potentially allow access to the corresponding acetyl product **2.21**, but unfortunately, the aldehyde product **2.22** was isolated instead. It has been well-documented that either the aldehyde or the ketone are possible products in a Wacker oxidation reaction, whereby steric influence and as well as coordination to heteroatoms may lead to a reversal of the regiochemistry in this type of reaction.[101]



Scheme 2.2.6. Various Methods Employed in the Addition Reaction.

In both instances using both the vinyl and isopropenyl Grignard reagents, the addition product and the starting ketone were inseparable by chromatography. Therefore, to separate the mixture of starting material and product, we reduced the ketone with $NaBH_4$ and separated the mixture by chromatography. Separation was possible between the desired product and alcohol **2.17**. Alcohol **2.17** could be recovered and then re-oxidized using IBX to afford ketone **2.18** that could be used once again in the addition with the Grignard reagent to generate alcohol **2.19** (Scheme 2.2.6.).

A number of different reaction conditions were examined and the results are summarized below (Table 2.2.2.). In most instances, an excess of Grignard reagent had to be used along with prolonged reaction times. The yields for this reaction remained low and unreacted starting material remained. After a number of attempts at optimizing reaction conditions, we were fortunate to discover that by pre-mixing $CeCl_3$ with ketone **2.18** for a short period of time followed by the additon of the Grignard reagent at low temperature, all the starting material could be fully converted to the product alcohol **2.19**. Under these optimized conditions, the product yield was 80% and an 87:13 ratio of stereoisomers was produced with the major isomer being the desired one. This method, developed by Inamura and co-workers,[102] showed that activation of the carbonyl with $CeCl_3$ is important prior to the addition of the Grignard reagent. Coordination of $CeCl_3$ with the carbonyl oxygen will activate the carbonyl center, thus making it more electrophilic and more susceptible to 1,2-addition by the Grignard reagent rather than enolate formation.

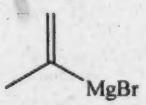
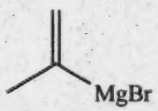
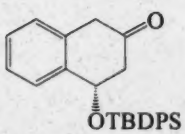
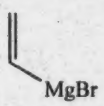
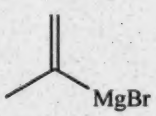
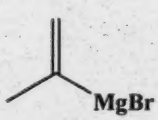
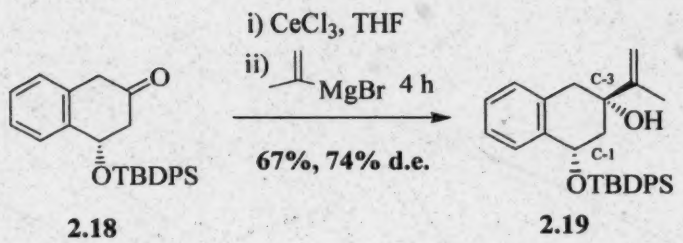
Starting Material	Cerium(III) chloride	Organometallic Reagent	Reaction Time	Yield
	N/A	 2 equiv	24 h	0%
	10 equiv.	 1.5 equiv	24 h	50% + 50% Starting Material
 2.18	10 equiv.	 5 equiv	24 h	50% + 50% Starting Material
	7 equiv.	 2.2 equiv	2 days	66%
	3.5 equiv.	 **1.8 equiv**	**4 h**	**80%**

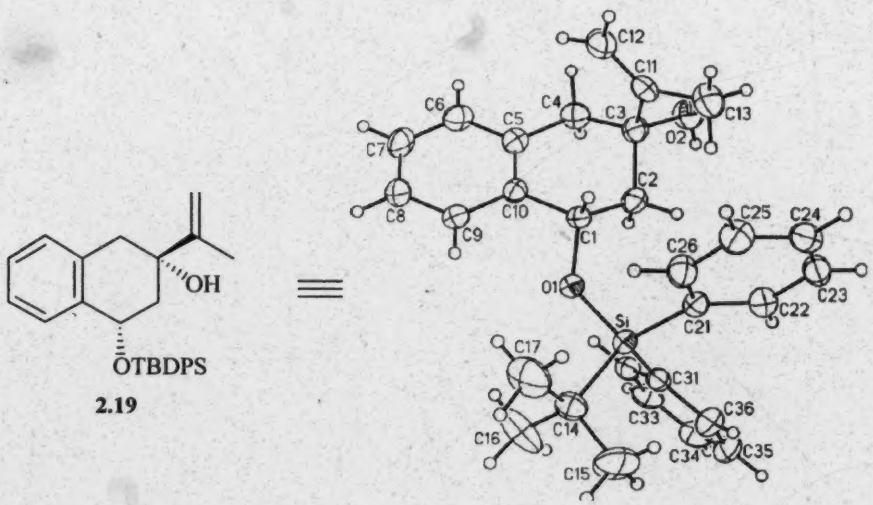
Table 2.2.2. Summary of Addition Reaction Conditions for Ketone **2.18**.



2.18 **2.19**

Scheme 2.2.7. Optimized Reaction Conditions for Grignard Addition Reaction.

To establish the relative stereochemistry at C-1 and C-3, a X-ray single crystal structure of **2.19**[103] was obtained (Figure 2.2.1.).[103] The isopropenyl group is oriented pseudo axially, while the OH group is cis with respect to the –OTBDPS group. Having verified the relative stereochemistry at C-1 and C-3, our attention was focused on the introduction of the carbonyl group.



2.19

Figure 2.2.1. Single Crystal X-Ray Structure of Alkene **2.19**.[103]

Ozonolysis was carried out to afford ketone **2.20** and different reaction conditions were examined to open the intermediate ozonide ring. These methods included the use of (a) Me_2S,[104] (b) PPh_3[105] and (c) Et_3N[106] (Table 2.2.3.) and (Scheme 2.2.8.). All these methods led to ketone **2.20**; however, Et_3N consistently provided better yields. In the original report of the use of this reagent to covert ozonides to carbonyl compounds, the authors proposed that upon reaction with base, this led to the removal of a methylene proton that generates the carbonyl product along with a formate anion.[106]

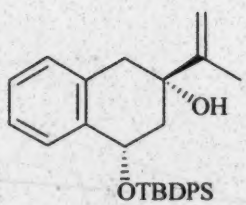
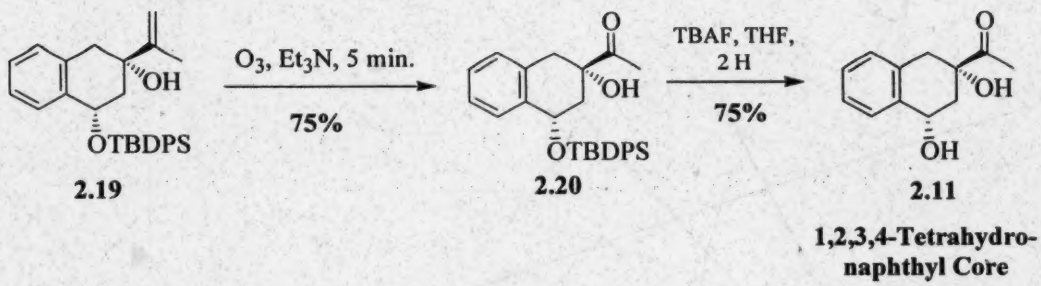
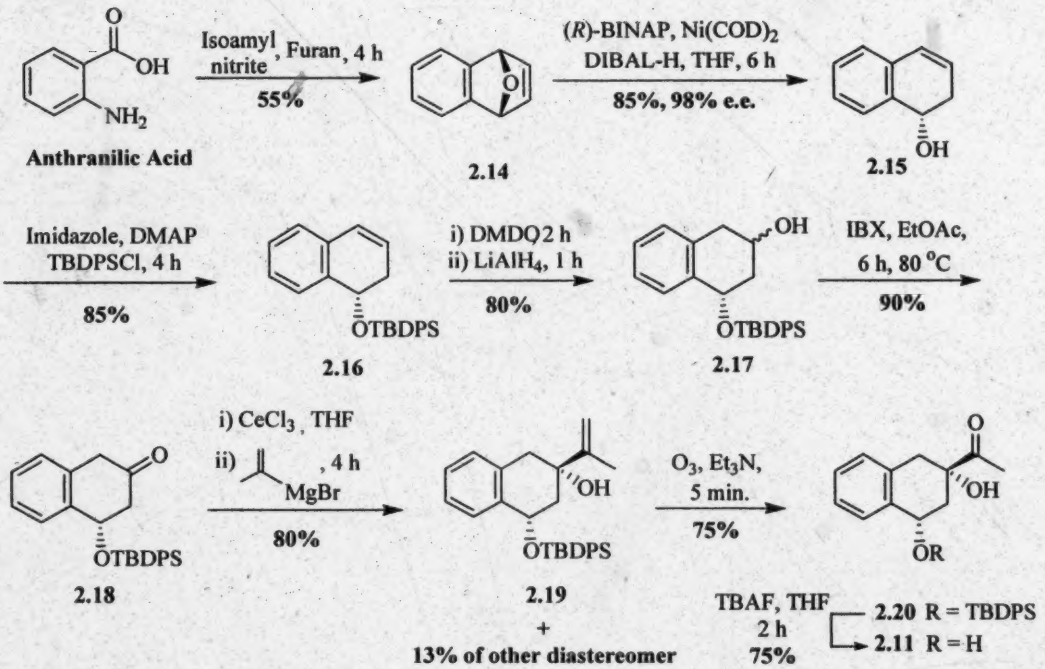
Starting Material	Conditions	Yield
	i) O_3 ii) Me_2S	30%
 **2.19**	i) O_3 ii) PPh_3	50-70%
	i) O_3 **ii) Et_3N**	**75%**

Table 2.2.3. Reaction Conditions Used for the Ozonolysis of Alkene **2.19**.



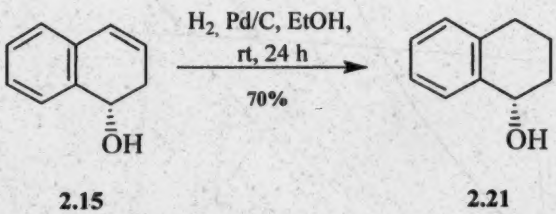
Scheme 2.2.8. Final Sequence Towards Naphthyl Target.

Removal of the silyl protecting group with TBAF provided the final 1,2,3,4-tetrahydro-napthyl core **2.11** with an overall of yield of 75%. A summary of the synthetic sequence for this target is shown below (Scheme 2.2.9.). Starting from anthranilic acid, the target, 1,2,3,4-tetrahydro-napthyl core could be obtained in nine steps with an overall yield of 14%



Scheme 2.2.9. Synthetic Sequence for the 1,2,3,4-Tetrahydro-naphthyl Core.

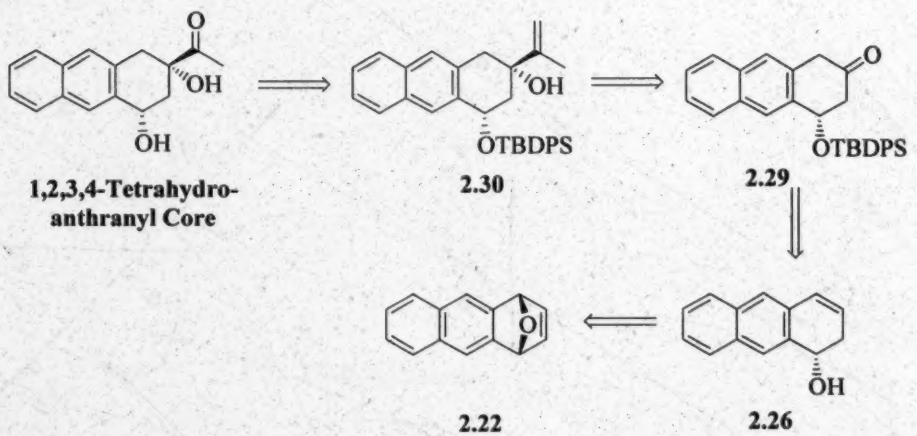
Compound **2.15** was also hydrogenated using Pd/C and H_2 to afford alcohol **2.21**.[107,108] A glycosylated version of this compound served as a control in the cytotoxicity studies reported later.



Scheme 2.2.10. Hydrogenation of (*S*)-(1H,2H)-dihydronaphthalen-1-ol **2.21**.

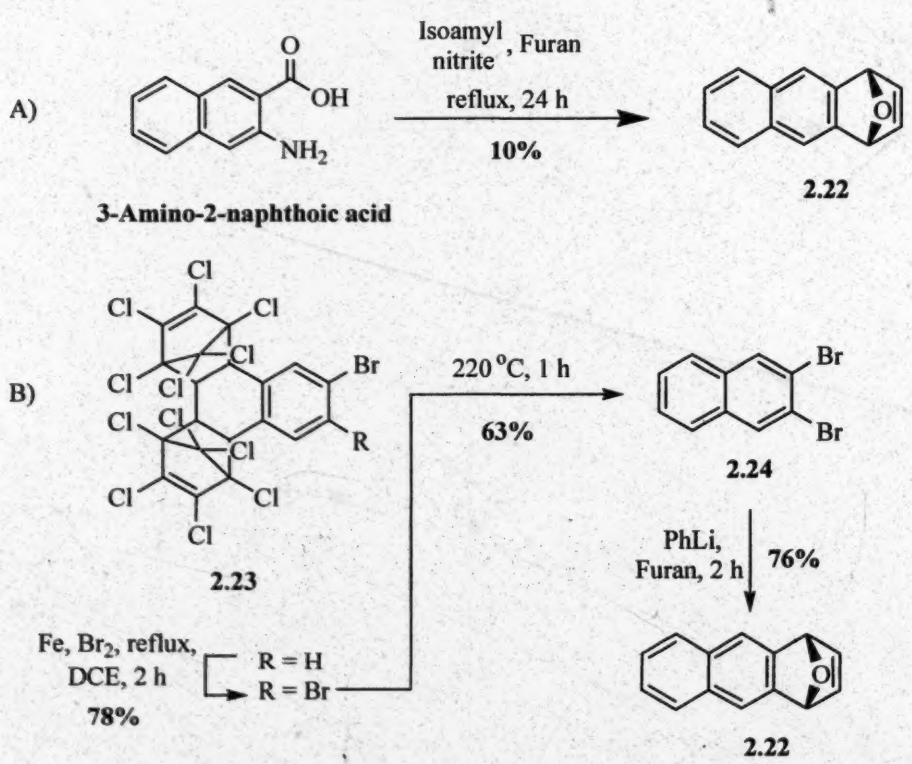
2.3. Synthesis of the 1,2,3,4-Tetrahydro-anthranyl Core

The preparation of the anthranyl core was slightly more challenging than we had anticipated. The two aglycone cores are nearly identical with the exception that the anthranyl component possess an extra aromatic ring as compared to the naphthyl component. The retrosynthesis involved similar intermediates as that of the naphthyl core (Scheme 2.3.1.), where alcohol **2.30** would serve as the precursor to the target molecule. This alcohol **2.30** could be prepared from ketone **2.29**, and this ketone would arise from the secondary alcohol **2.26**. This alcohol could be prepared via the corresponding oxatricyclic compound **2.22**.



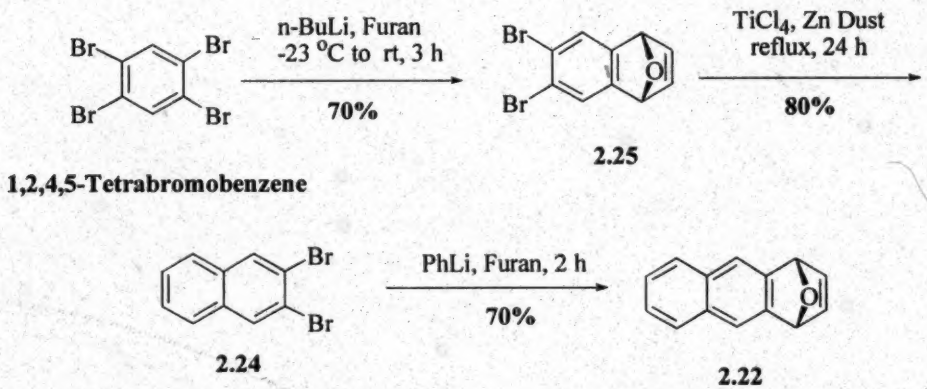
Scheme 2.3.1. Retrosynthesis of the 1,2,3,4-Tetrahydro-anthranyl Core.

Because we wanted to use the nickel catalyzed asymmetric reductive ring opening reaction of oxacyclic olefins, our starting material would then have to be the oxatricyclic alkene precursor **2.22**. Two different methods were initially evaluated to prepare this system, but these methods were tedious and often led to low yields. In the first method (Scheme 2.3.2.), (A),[86] 3-amino-2-naphthoic acid was reacted with isoamyl nitrite and furan to afford **2.22**, but the yield of this reaction was only 10%. In method (B),[109] using adduct **2.23**, bromination at the ortho position provided the product with 78% yield followed by pyrolysis, which led to 2,3-dibromonaphthalene **2.24** with an overall yield of 63%. However, during the pyrolysis reaction, the yield of product **2.24** was inconsistent.



Scheme 2.3.2. Initial Attempts for the Preparation of Oxatricyclic Alkene **2.22**.

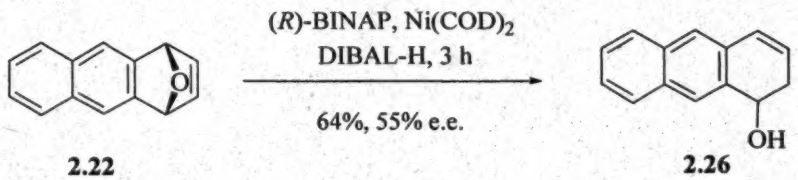
Realizing the difficulty in preparing alkene (2.22) we examined a different method, developed by Hart and co-workers[110] which employs the use of 1,2,4,5-tetrabromobenzene (Scheme 2.3.3.). This three-step protocol includes a Diels-Alder reaction, a dehydration and another Diels-Alder cycloaddition[111] that led to compound **2.22**.



Scheme 2.3.3. Improved Synthesis of Oxatricyclic Alkene **2.22**.

Thus, 1,2,4,5-tetrabromobenzene was treated with *n*-BuLi and furan to afford product **2.25** via a Diels-Alder reaction in 70% overall yield. Dehydration was carried out in the presence of $TiCl_4$ and Zn yielding 2,3-dibromonaphthalene[110] **2.24** in 80% yield and this compound could be further converted to the oxatricyclic compound **2.22** in 70% yield via another Diels-Alder reaction using PhLi and furan.[111] The overall yield of this three-step sequence was 39%.

Compound **2.22** was then converted to alcohol **2.26** through the same nickel catalyzed asymmetric reductive ring opening reaction[85] that was employed in the naphthyl core synthesis. Unfortunately, after numerous attempts at controlling reaction time, amount of nickel catalyst and (*R*)-BINAP used, the best result obtained was only a yield of 64% and an e.e of 55% as determined by chiral HPLC (Table 2.3.1.).



2.22 **2.26**

Scheme 2.3.4. Preparation of Alcohol **2.26**.

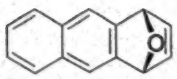
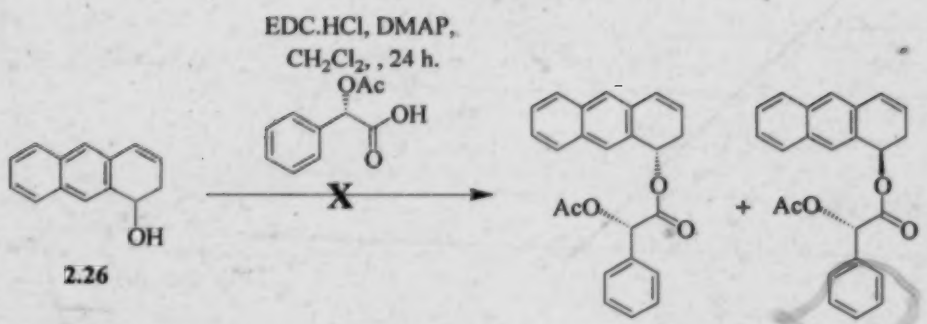
Starting Material	$Ni(COD)_2$	*R*-BINAP	Reaction Time	Yield, % e.e
	7%	11%	6 h	54%, 55%
	7%	11%	4 h	40%, 51%
 2.22	14%	22%	6 h	30%, 74%
	10%	18%	3 h	52%, 53%
	10%	**18%**	**2.5 h**	**64%, 55%**

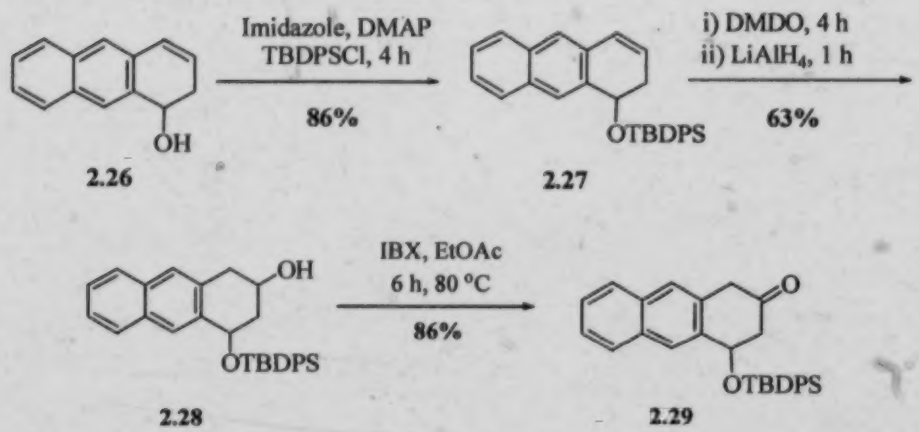
Table 2.3.1. Summary of Nickel/(*R*)-BINAP Catalyzed Reaction of Oxatricyclic Alkene **2.22**.

In most cases, prolonged reaction times led to low yield with good e.e., while shorter reaction times led to better yield and lower e.e. We opted to do the reaction under conditions that gave higher yield and lower e.e.. This required resolution of the enantiomeric mixture and we attempted to this by esterification of the secondary alcohol with *S*-acetyl-mandelic acid. Unfortunately this was unsuccessful and decomposition of starting material was observed instead (Scheme 2.3.5.).[82]



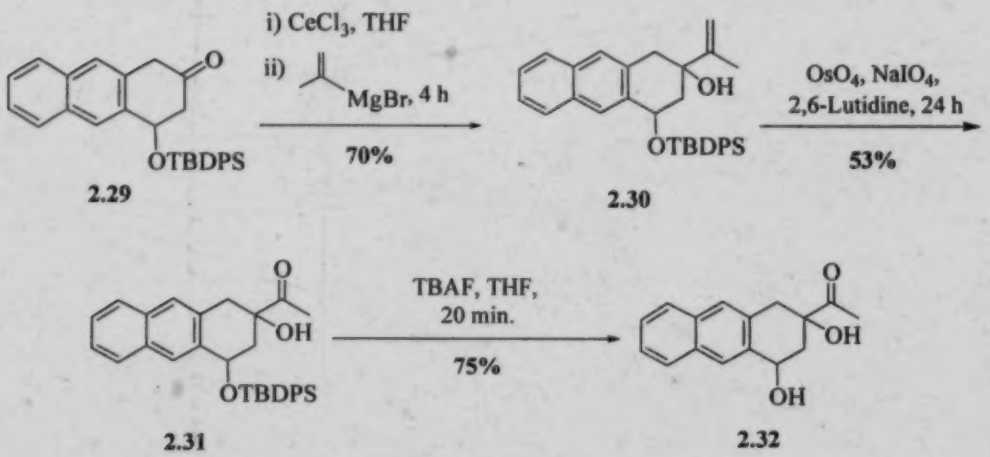
Scheme 2.3.5. Attempted Resolution of Alcohol **2.26** with *S*-acetyl-mandelic Acid.

Because the two enantionmers could not be resolved, the subsequent synthetic steps were carried out as a mixture. Alcohol **2.26** was protected as the TBDPS ether **2.27**[85] and subjected to epoxidation[93] followed by ring opening of the epoxide[91] and oxidation[96] of the alcohol to yield ketone **2.29** (Scheme 2.3.6.). This four-step sequence provided ketone **2.29** with an overall yield of 47%.



Scheme 2.3.6. Preparation of Ketone **2.29**.

A new stereogenic center was formed once the isopropenyl group was added to the carbonyl upon reacting with isopropenylmagnesium bromide and $CeCl_3$.[102] Two isomers were obtained with an overall yield of 70% and a ratio of 85:15. We assumed that the enatioselectivity with the Lautens approach would be the same as in the case for the anthranyl system. In any case, we compared the ^1H NMR data for compounds **2.28** to **2.30** with that of the naphthyl analogs of **2.17** to **2.19**, and based on both splitting patterns and chemical shifts, which were very similar in both cases, we believed we had the right pair of enantionmers. The major isomer of **2.30** was used in subsequent reaction steps. Attempts to ozonolyze[105, 106] the alkene were unsuccessful, but rather, a variant of the Lemieux-Johnson reaction was carried out using OsO_4, $NaIO_4$ and 2,6-lutidine[112] to afford the desired ketone **2.31** in 53% overall yield. Deprotection of the secondary alcohol using TBAF gave the final product **2.32** in 75% as a mixture of enantiomers. (Scheme 2.3.7.).

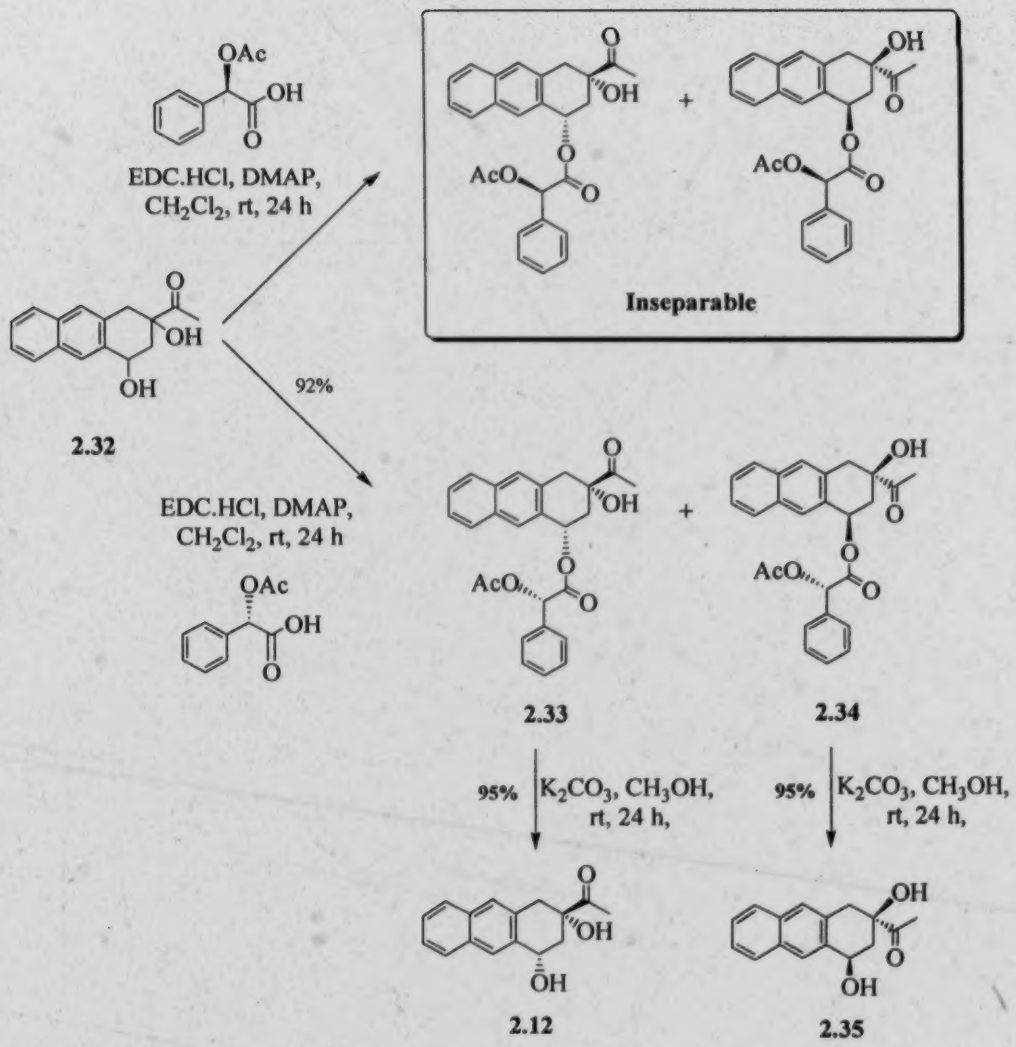


Scheme 2.3.7. Final Sequence Towards Compound **2.32**.

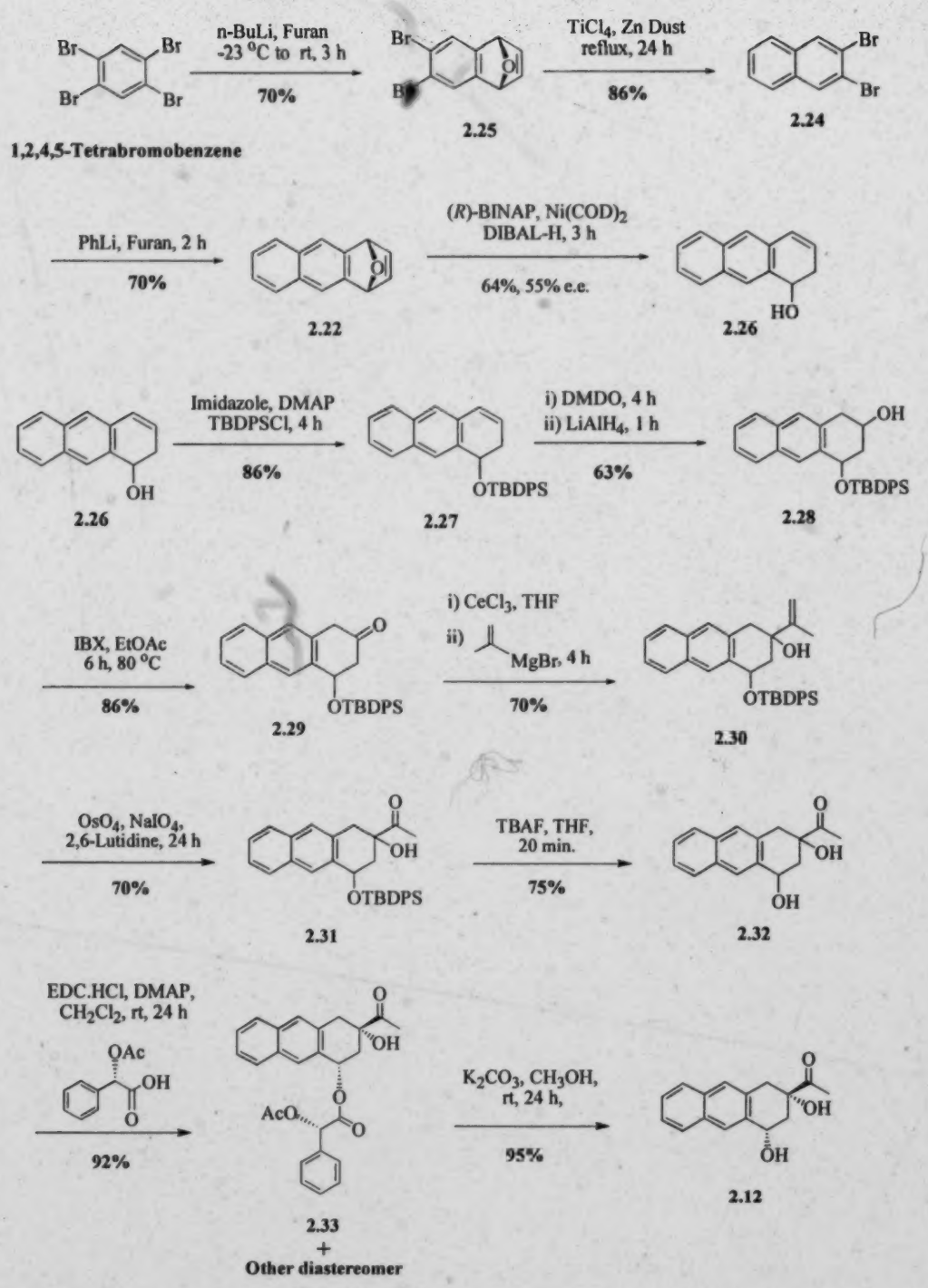
2.3.1. Resolution of the 1,2,3,4-Tetrahydro-anthranyl Core

To separate the mixture of enantiomers **2.32**, we chose to esterify the secondary alcohol with either the *S*-acetyl-mandelic acid or the *R*-acetyl-mandelic acid (Scheme 2.3.8.). Esterification of the secondary alcohol with *S*-acetyl-mandelic in the presence of EDC·HCl and DMAP[82] led to two diastereomers in 92% overall yield that were easily separable via column chromatography. In contrast, esterification with *R*-acetyl-mandelic acid, did not yield separable products. Removal of the chiral auxiliary with K_2CO_3 led to the two enantiomers in 95% yield and their optical rotations were obtained. The optical rotation for compounds **2.12** and **2.35** were obtained and their values were $[\alpha]_D$ +18.2 and $[\alpha]_D$ -12.0 respectively.

A summary of the synthetic sequence for this target is shown in Scheme 2.3.9. where the 1,2,3,4-tetrahydoanthranyl core was obtained in 14 steps starting from 1,2,4,5-tetra-bromobenzene with an overall yield of 4%



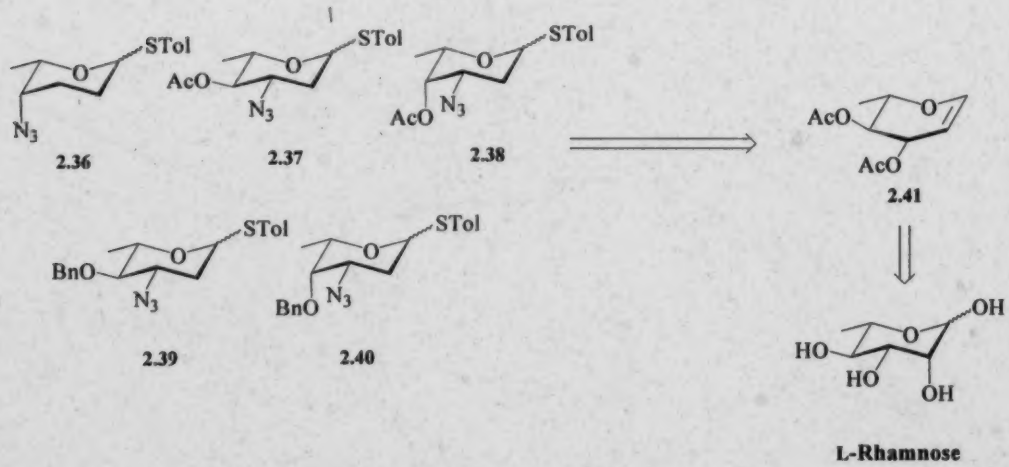
Scheme 2.3.8. Resolution of Compound **2.12** with *R/S*-acetyl-mandelic Acids.



Scheme 2.3.9. Synthetic Scheme for the 1,2,3,4-Tetrahydro-anthranyl Core.

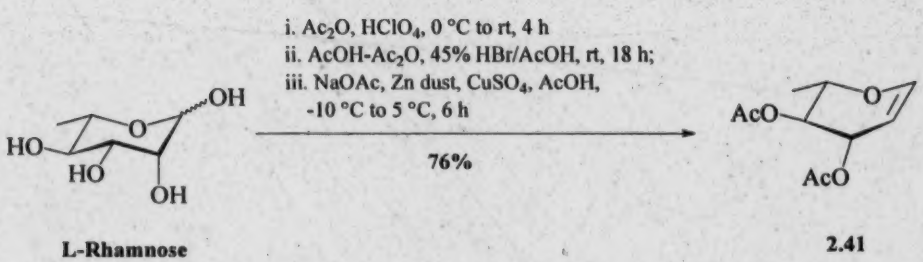
2.4. Syntheses of the Monosaccharide Donors

Having obtained the aglycone, we next focused on the preparation of the carbohydrate donors. Five monosaccharide donors were envisioned, which could be prepared from 3,4 di-*O*-acetyl-L-rhamnal, which in turn can be produced from L-rahmnose (Scheme 2.4.1.).



Scheme 2.4.1. Retrosynthesis of Monosaccharide Donors.

L-Rhamnose was subjected to a three-step protocol[112,113] (Scheme 2.4.2.), that led to glycal **2.41**. This protocol included protecting hydroxyl groups as acetates using Ac_2O and $HClO_4$, followed by bromination at the anomeric center using HBr-acetic acid, and subsequent treatment with zinc dust, cupric sulphate pentahydrate, and NaOAc to lead to **2.41** in 76% overall yield in three steps. This glycal intermediate serves as the building block for all five monosaccharide donors.

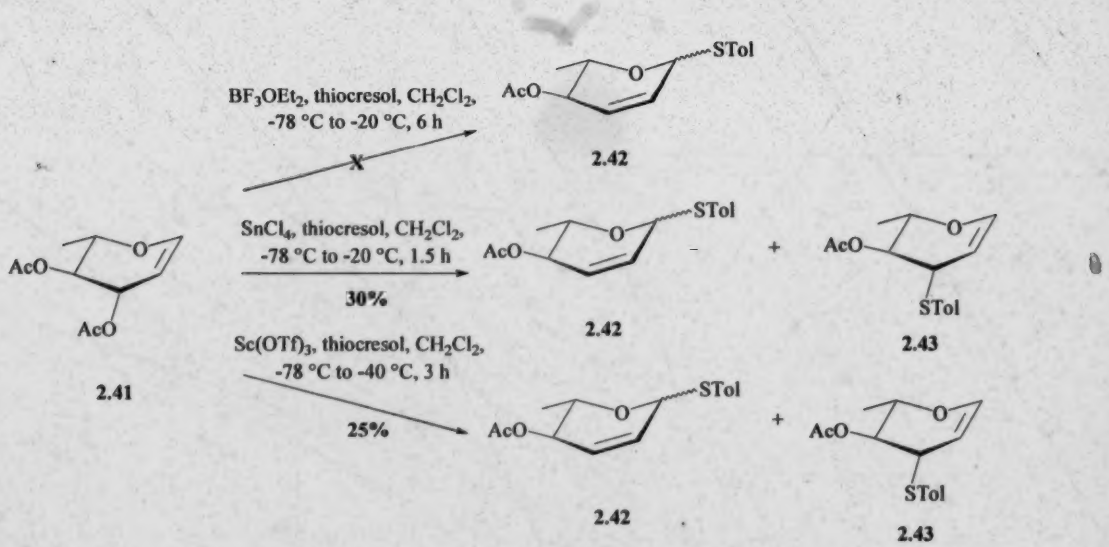


L-Rhamnose **2.41**

Scheme 2.4.2. Preparation of Building Block Glycal.

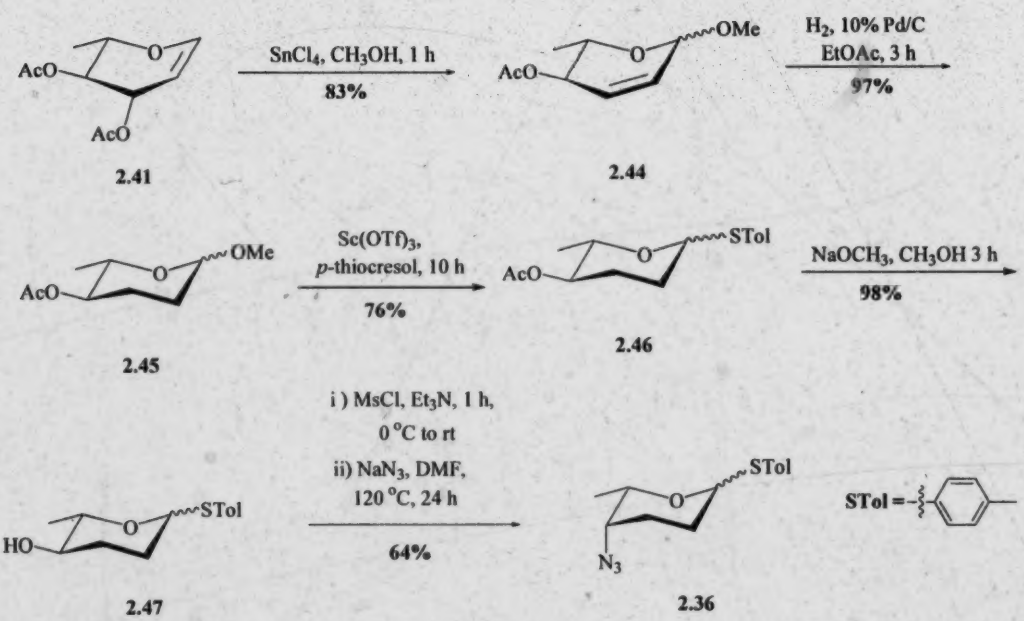
2.4.1 Synthesis of Monosaccharide Donor **2.36**

The synthesis of donor **2.36** was initially attempted as shown in Scheme 2.4.3. where a Ferrier reaction was attempted on glycal **2.41** to generate thioglycoside **2.42**. In the presence of BF_3OEt_2 and *p*-thiocresol, decomposition of starting material was observed, while using $SnCl_4$ as the Lewis acid, the desired thioglycoside was obtained in only 30% yield along with large amounts of undesired product **2.43** in which the thio group added to C-3. To overcome this problem, a milder Lewis acid was used. In the presence of $Sc(OTf)_3$,[114] the formation of the side-product was suppressed, but the yield was only 25%. Prolonged reaction times led to decomposition of starting material, and therefore another method was examined.



Scheme 2.4.3. Synthesis of Thioglycoside **2.42**.

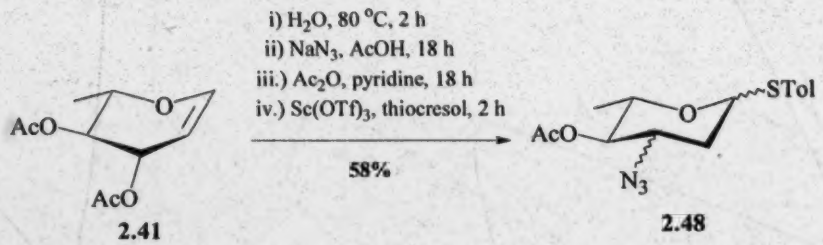
Our solution to this problem (Scheme 2.4.4.) involved the preparation of the methyl glycoside **2.44** initially through a Ferrier rearrangement using $SnCl_4$ and methanol followed by hydrogenation using Pd/C and H_2 to give **2.45** in 81% yield over two steps. Having this compound in hand, treatment with *p*-thiocresol and $Sc(OTf)_3$ was then used to obtain thioglycoside **2.46** with a 76% yield. Removal of the acetate group at the 4-position using sodium methoxide and methanol gave alcohol **2.47** in quantitative yield. Monosaccharide donor **2.48** was obtained by first converting the alcohol to the mesylate followed by treatment with sodium azide to afford the product in 64% yield as a 6:1 α/β mixture.



Scheme 2.4.4. Synthesis of Monosaccharide Donor **2.36**.

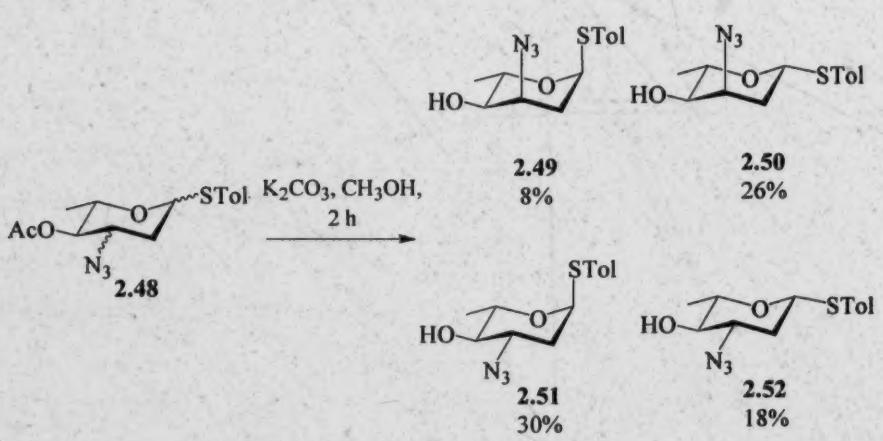
2.4.2. Syntheses of Monosaccharide Donors **2.37** and **2.38**.

Glycal **2.41** was also the precursor to the monosaccharide donors **2.37** and **2.38** (Scheme 2.4.5.). Treatment of glycal **2.41** with H_2O at 80 °C followed by the addition of sodium azide afforded a mixture of 3-azido-2,3,6-trideoxy-L-arabino/ribopyranoses.[115] The alcohol at the anomeric center was protected as an acetate, and treatment of the resulting product with $Sc(OTf)_3$[114] and thiocresol afforded thioglycoside **2.48** in 58% overall yield in 4 steps. This mixture of products could not be separated by chromatography and subsequent reactions had to be carried out before separation could be achieved. [113]



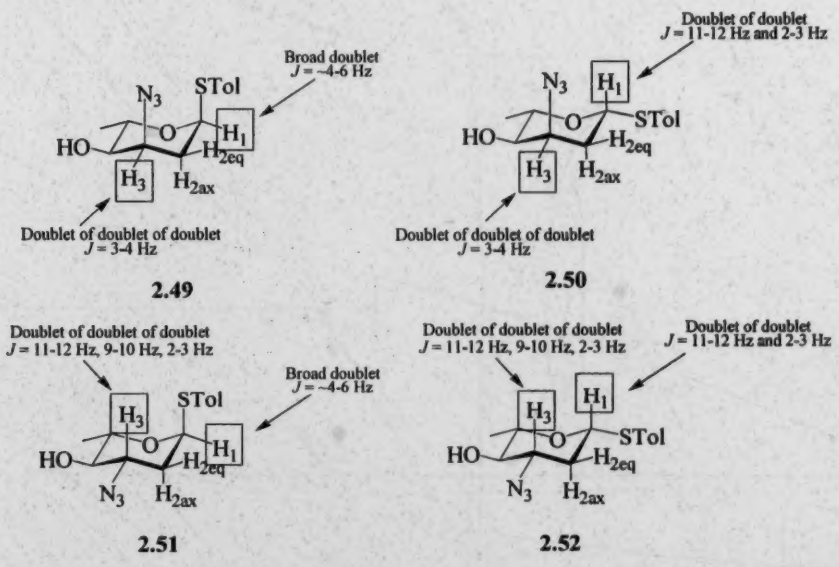
Scheme 2.4.5. Preparation of **2.48**.

After removal of the acetate group at the 4 position, separation of the isomers were possible by chromatography (Scheme 2.4.6.). Four isomers were obtained, both undesired α and β ribpyranose analogs **2.49** and **2.50** in 32% yield, and as well as the desired α and β arabinopyranose donors **2.51** and **2.52** in 48% yield. The ratio of the ribose donors to arabinose donors was 1:1.5.



Scheme 2.4.6. Separation of the Arabinose and Ribose Isomers.

To confirm that we had isolated the right pair of carbohydrate donors, we compared the coupling constant using Karplus relations between H-1 and H-2 to differentiate between the α and the β products, and also H-2 and H-3 to differentiate between ribose and arabinose donors (Figure 2.4.1.). In any case, the α product would appear as a broad doublet in the ^{1}H NMR spectrum with an average *J* value of ~4-6 Hz between H-1 and H-2_{ax}/H-2_{eq}. The β product appeared as a doublet of doublet with *J* values of ~11-12 Hz between H-1 and H-2_{ax}, while ~ 2-3 Hz between H-1 and H-2_{eq}. The coupling pattern between H-2 and H-3 for the ribose analogs appeared as a doublet of doublet of doublet and the average *J* value measured between H-1 and H-2_{ax}, H-2_{eq} and H-4 was ~3-4 Hz. The coupling pattern between H-2 and H-3 for the arabinose analogs appeared as a doublet of doublet of doublet. *J* values of ~11-12 Hz between H-2_{ax} and H-3 and also ~9-10 Hz between H-3-and H-4 was measured while a smaller *J* value of ~2-3 Hz between H-2_{eq} and H-3 was also recorded. All of these results together helped us to establish the four different types of isomers obtained.

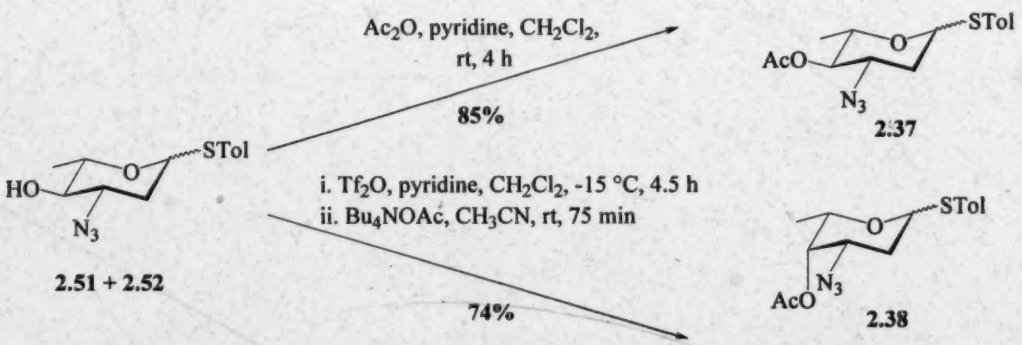


2.49 **2.50**

2.51 **2.52**

Figure 2.4.1. *J* values for H-1 and H-3 of Ribose and Arabinose Compounds.

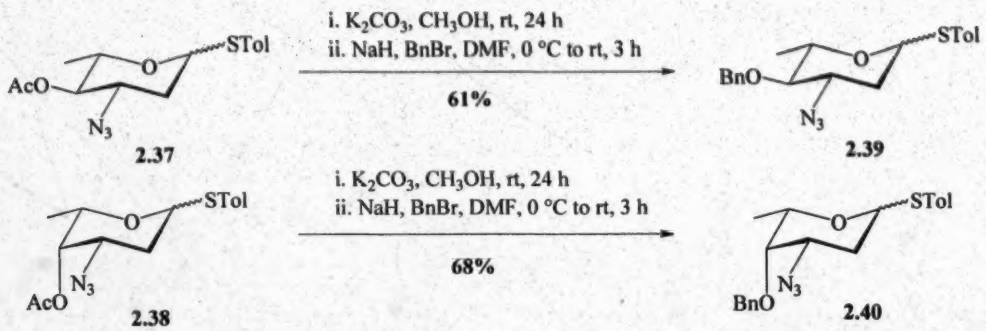
Having sugar donors **2.51** and **2.52** in hand, installation of an acetate group at the 4-position afforded monosaccharide donor **2.36** in 85% overall yield. As well, this compound could be treated with triflic anhydride followed by the addition of tetrabutylammonium acetate[116] to yield monosaccharide donor **2.37** in 74% yield over two steps (Scheme 2.4.7.).



Scheme 2.4.7. Preparation of Monosaccharide Donors **2.36** and **2.37**.

2.4.3. Syntheses of Monosaccharide Donors **2.39** and **2.40**.

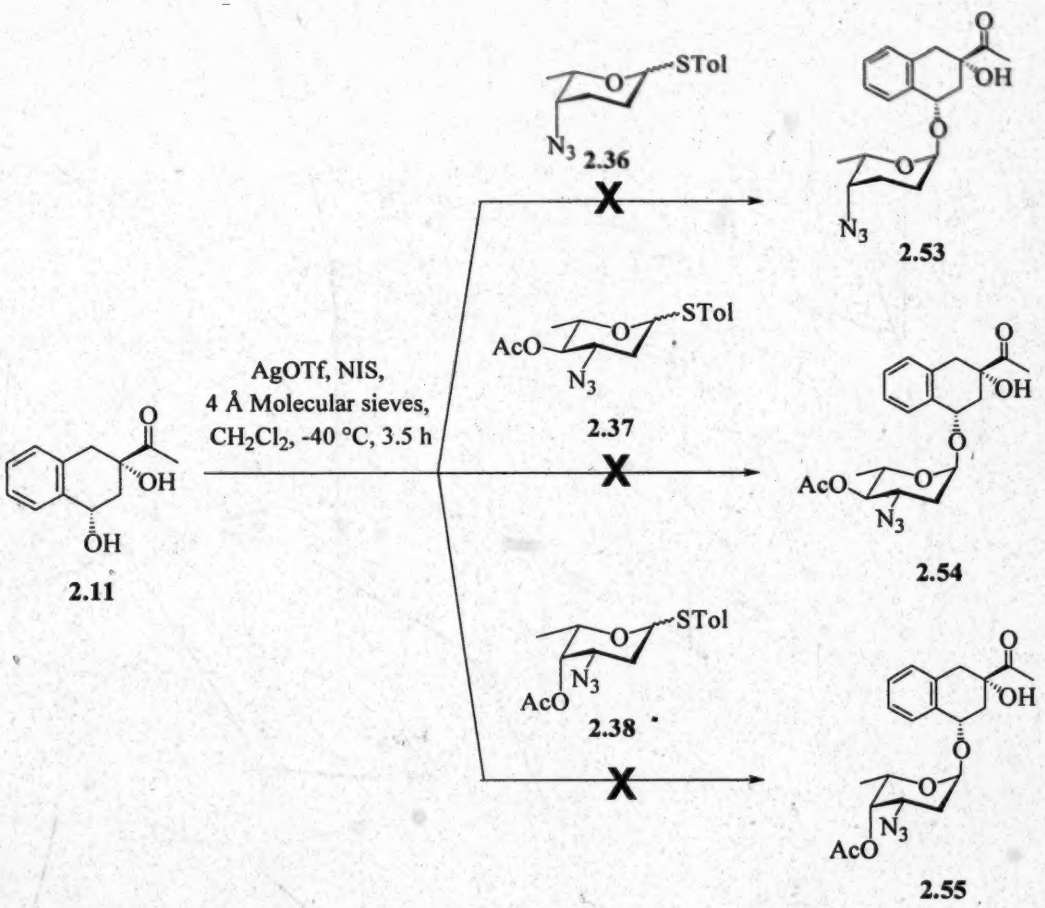
Two other analogs having a benzyl group at the 4-position were prepared from **2.37** and **2.38**. Removal of the acetate group at the 4-position using K_2CO_3 followed by treatment with NaH and benzyl bromide afforded **2.39** and **2.40** in 61% and 68% yield over two step. (Scheme 2.4.8.).



Scheme 2.4.8. Preparation of Monosaccharide Donors **2.39** and **2.40**.

2.5. Synthesis of 1,2,3,4-Tetrahydro-naphthyl Glycosides

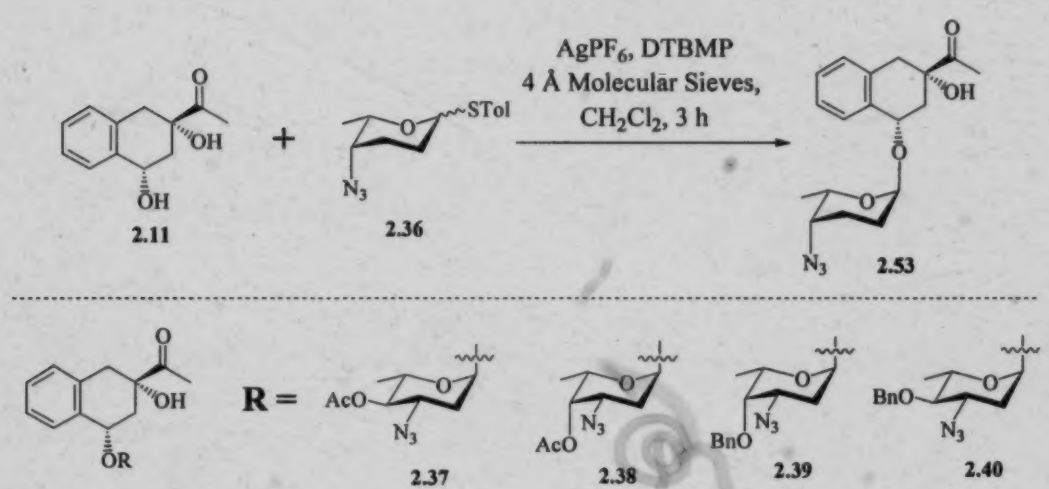
The initial protocol we chose to use for glycosylating the thioglycoside donor with the alcohol acceptor was with AgOTf and NIS.[117] However, the glycosylation reactions using the naphthyl core with monosaccharide donors **2.36**, **2.37**, and **2.38** as the standard did not lead to any product. Decomposition of the naphthyl core was observed along with carbohydrate donors having been hydrolyzed (Scheme 2.5.1.).



Scheme 2.5.1. Initial Glycosylation Reactions Using AgOTf and NIS.

It may be possible that under these reaction conditions, the acceptor may have decomposed due to the mildy acidic nature of the reaction media. The thioglycoside donors were also hydrolyzed to their corresponding reducing sugar, as water may have been present in the reaction mixture. Even though the synthesis of 2-deoxy-glycosides has been extensively studied,[118] none of the conditions previously described seemed to be an effective solution in the glycosylation of our target compounds.

By switching to neutral conditions[119] with the use of $AgPF_6$ and DTBMP, this problem of acceptor decomposition could be circumvented. Using the tetrahydro-naphthyl core as the standard once again, the glycosylation reaction with all five monosaccharide donors were carried out successfully (Scheme 2.5.2.). The products were obtained in yields of 45-85% depending on the type of monosaccharide donors used; these results are summarized in Table 2.5.1.



Scheme 2.5.2. Glycosylation Reactions Using $AgPF_6$ and DTBMP for the Naphthyl Core.

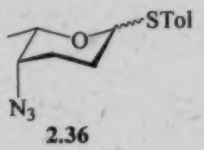
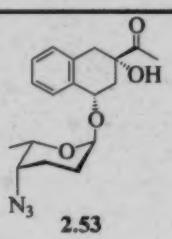
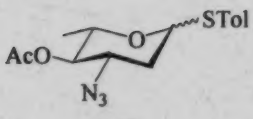
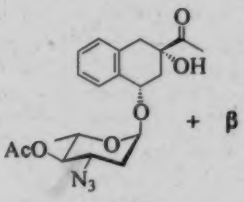
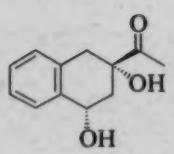
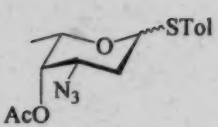
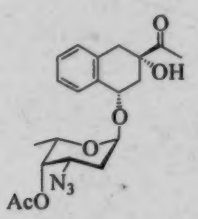
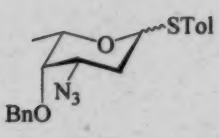
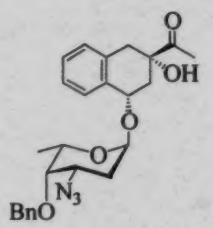
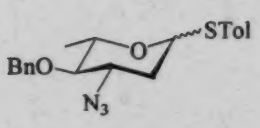
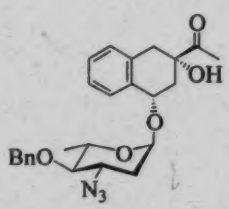
Acceptor	Donor	Product	Yield
	 2.36	 2.53	85% α
	 2.37	 2.54	39% α + 31% β
 2.11	 2.38	 2.55	70% α
	 2.39	 2.56	60% α
	 2.40	 2.57	46% α

Table 2.5.1. Summary of Glycosylation Reactions for the Tetrahydro-naphthyl Core.

To confirm that we had indeed obtained the α product, we once again measured the *J* values between H-1 and H-2_{ax}/H-2_{eq} of the carbohydrate moiety for all glycosylated products. In all cases, the ^{1}H NMR spectrum showed that H-1 appeared as a doublet, and had an average *J* value of ~3-4 Hz between H-1 and H-2_{ax}/H-2_{eq}. With sugar donor **2.37**, both the α and β products were obtained, and for the β product, H-1 appeared as a doublet of doublet with a *J* value of 9.6 Hz between H-1 and H-2_{ax}, and a value of 1.9 Hz between H-1 and H-2_{eq}. With these *J* values, it enabled us to confirm that the glycosylation reaction using $AgPF_6$ and DTBMP proceeded with excellent α selectivity.

It has been shown that by performing glycosylation reaction using $AgPF_6$ and DTBMP, the results tend to give high α selectivity. In the case for our substrate, product formation led exclusively to the α product in most case, with the exception of monosaccharide donor **2.37**, where a 3:2 α:β mixture of products were obtained. The poor selectivity associated with the formation of the β isomer could be explained based on previous study made by the Demchenko group[120] and others,[121] that a remote participation effect could occur in monosaccharide that possesses a participating moiety (e.g., ester groups) at C-4. If we consider the mechanism of this reaction (Figure 2.5.1.) one could observe that during the formation of the oxocarbenium ion, a conformational change can occur from a $^1C_4$ to a $^4C_1$ conformation via a ring flip. This result will flip the acetate group at the C-4 position from equatorial to axial, and this new conformation could allow the acetate group to participate forming a dioxolium ion in a boat conformation. Attack of the alcohol at the anomeric center, followed by another ring flip, will lead to the corresponding β product. It is assumed that these ring-flipped conformations are present, as typically deoxy monosaccharides are more flexible than their fully oxygenated

counterparts. As well, in the case of our sugar donors, the methyl and azido substituents are not very bulky and if these groups were to flip from equatorial to axial, the unfavorable 1,3-diaxial interaction may not be so pronounced. One very interesting piece of evidence that supports this result is that by switching the protecting group from an ester **2.37** to a benzyl group **2.40**, only the α product is observed.

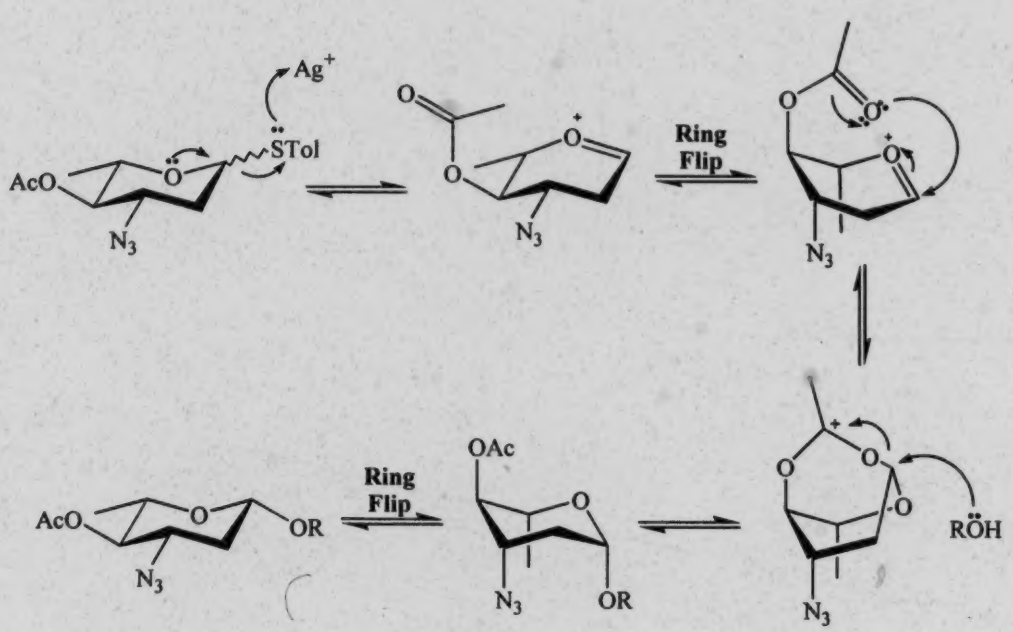
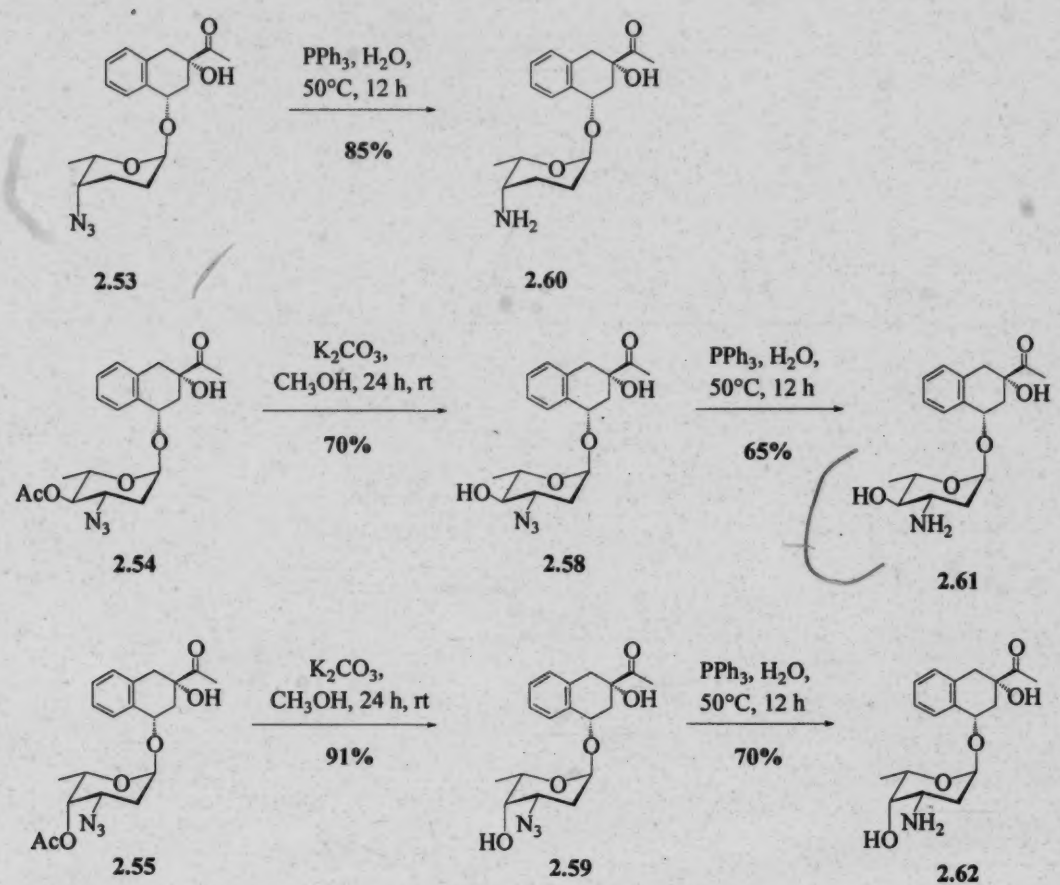


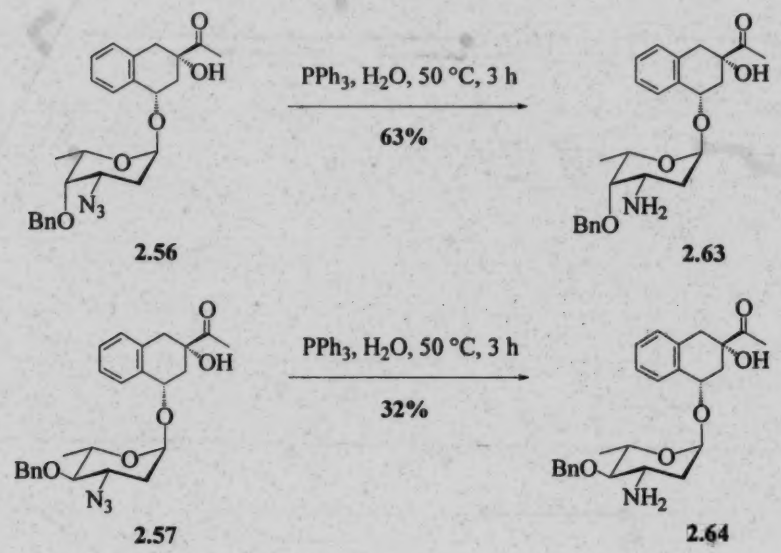
Figure 2.5.1. Proposed Mechanism for the Formation of the β Product of **2.54**.[120]

Having completed the glycosylation reactions, removal of the acetate group for compounds **2.54** and **2.55** with K_2CO_3 yielded the deprotected products **2.58** in 70% and **2.59** in 91% yield (Scheme 2.5.3.). Staudinger reduction of the azido group in the presence of PPh_3 and water[122] of **2.53**, **2.58**, and **2.59** gave the final naphthyl glycosides **2.60** in 85%, **2.61** in 70% and **2.62** in 65% overall yield.



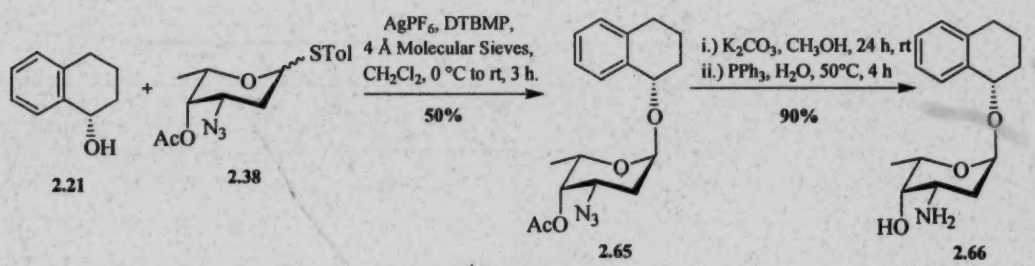
Scheme 2.5.3. Deprotection and Reduction Azido Group in 1,2,3,4-Tetrahydro-naphthyl Glycosides.

Reduction of the azido group[122] for compounds **2.56** and **2.57** were also completed and the yields for these compounds were 63% for **2.63** and 32% for **2.64** (Scheme 2.5.4.). The low yield associated with this reduction step for these benzyl derivatives are unclear.



Scheme 2.5.4. Reduction of Azido Group in 4-*O*-benzyl Analogs.

Tetrahydro-naphthyl core **2.21** was also glycosylated with monosaccharide donor **2.38** in the presence of $AgPF_6$ and DTBMP to yield **2.65** in 50% yield.[119] Deprotection and treatment with PPh_3 and water afforded the control naphthyl target **2.66** in 90% yield over two steps (Scheme 2.5.5.).

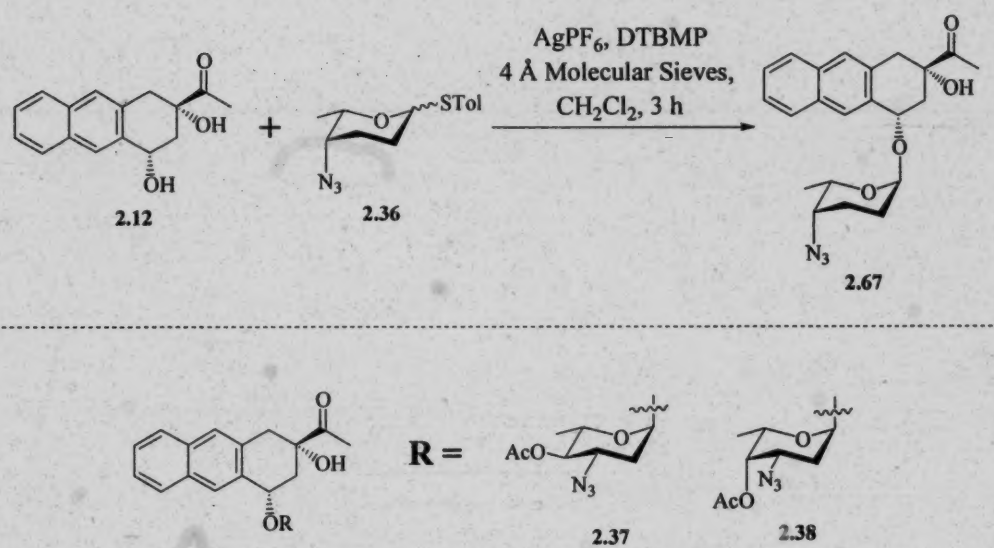


Scheme 2.5.5. Synthetic Sequence for Compound **2.66**.

2.6. Synthesis of 1,2,3,4-Tetrahydro-anthranyl Glycosides.

The anthranyl targets were prepared via the same strategy as the tetrahydro-naphthyl glycosides. Glycosylation reactions were carried out under neutral conditions using $AgPF_6$ and DTBMP[119] (Scheme 2.6.1.), and the yield of the products were nearly 50% for all three reactions (Table 2.6.1.). Once again, the β isomer of **2.68** was obtained as the minor product and this outcome could be accounted for via a similar mechanism (Figure 2.5.1.) as observed in the case for the naphthyl glycoside **2.54**. The reason for the low yield of this reaction was due to sugar donors having been hydrolyzed during the reaction, as water may have been present and therefore glycosylation could not take place and recovery of the alcohol acceptor was the case. If excess sugar donors (e.g.,

1.2 equiv. or more) were used in the reaction, glycosylation could take place at the tertiary alcohol position, and indeed this product was obtained and was characterized by both NMR and mass spectrometry. Previous work by Wang and co-workers whom of which also employed the same method of glycosylation as we did, showed that different sugar donors and alcohols used can lead to different yields in this type of reaction, and they have reported results which had low yields as well.[38]



Scheme 2.6.1. Glycosylation Reactions Using $AgPF_6$ and DTBMP for the Anthranyl Core.

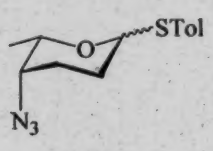
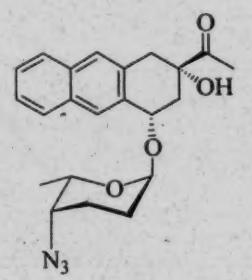
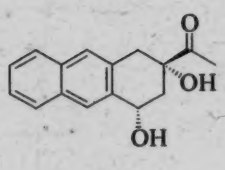
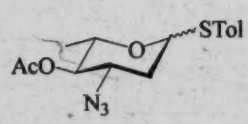
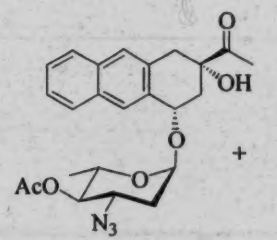
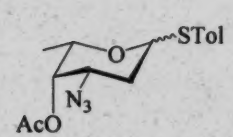
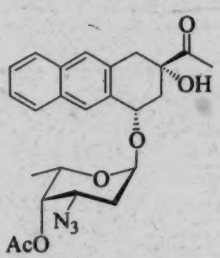
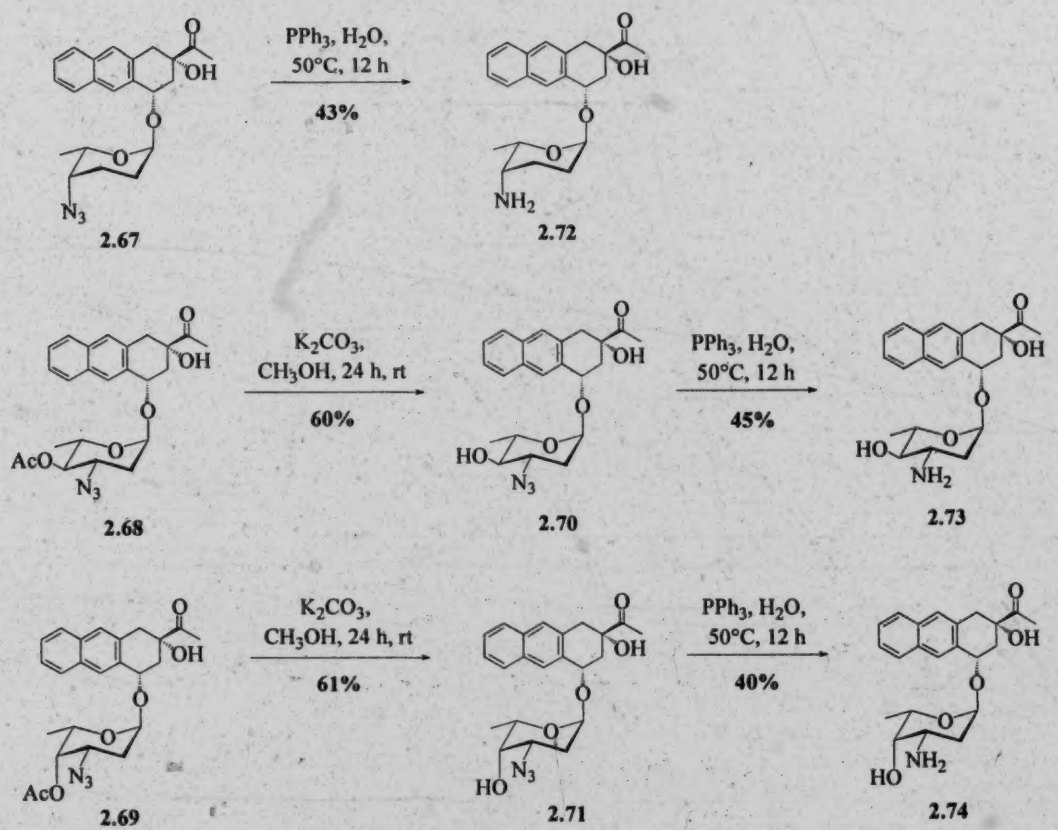
Acceptor	Donor	Product	Yield
	 2.36	 2.67	50% α
 2.12	 2.37	 2.68	+ β 31% α + 19% β
	 2.38	 2.69	52%

Table 2.6.1. Summary of Glycosylation Reactions for the Tetrahydro-anthranyl Core.

To confirm that we had indeed obtained the α product, just as in the case of the naphthyl glycosides, we once again measured the *J* values between H-1 and H-2_{ax}/H-2_{eq} of the carbohydrate moiety for all glycosylated products. In all cases, the ^{1}H NMR spectrum showed that H-1 appeared as a doublet, and had an average *J* value of ~3-4 Hz between H-1 and H-2_{ax}/H-2_{eq}, while with sugar donor **2.37**, a doublet of doublet was observed for H-1 and the *J* value measured was 9.6 Hz between H-1 and H-2_{ax} and 1.9 Hz between H-1 and H-2_{eq}.

Compounds **2.68** and **2.69** were subjected to deprotection with K_2CO_3 and methanol, and the yield of the products were 60% for **2.70** and 61% for **2.71**. Wang and co-workers have also demonstrated that for their types of system, which is similar to ours that during the deprotection step, low yield can occur, and these results are unclear. Reduction of the azido group for compounds **2.67**, **2.70** and **2.71** in the presence of PPh_3 and water[122] afforded the amino compounds with yields of 43% for **2.72**, 45% for **2.73** and 40% for **2.74** (Scheme 2.6.2.). The low yield associated with this reaction could be due to loss of final product during the purification step, as the compounds are quite polar and adhere onto silica gel.



Scheme 2.6.2. Deprotection and Reduction Azido Group in 1,2,3,4-Tetrahydro-anthranyl Glycosides.

In total, nine anthracycline mimetics were prepared and these compounds were screened for their cytotoxic activity against the MCF-7 cancer line (Figure 2.6.2.) by a coworker in the laboratory, Mr. Wei Shi.

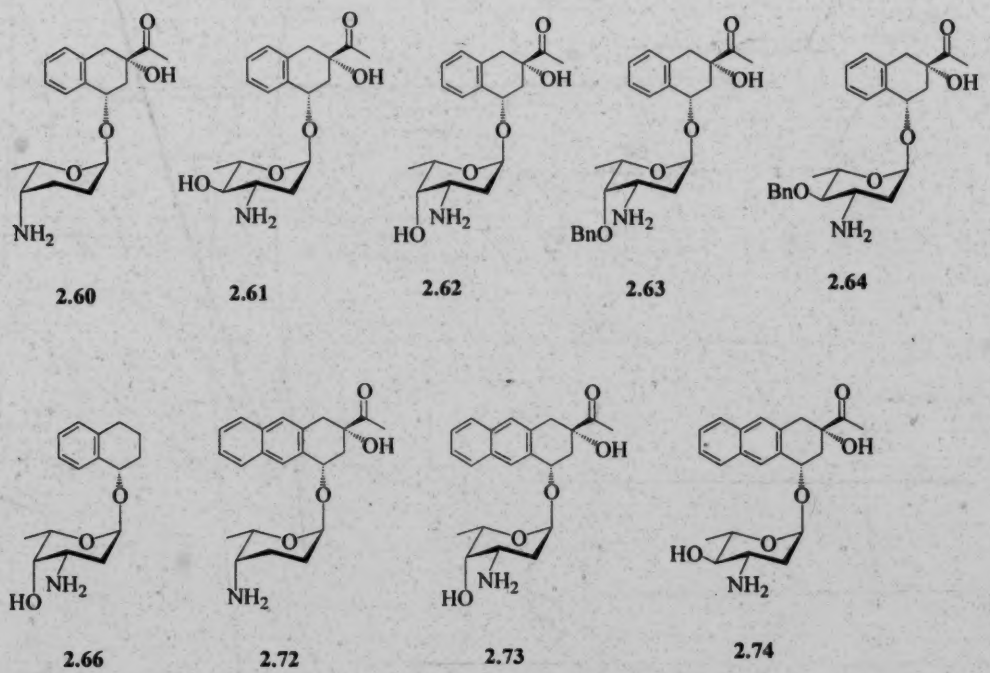


Figure 2.6.1. Target Compounds Used for Biological Screening.

2.7. Biological Evaluation and Cytotoxicity Assays

The nine compounds prepared were assayed against breast cancer cell line MCF-7 utilizing the PROMEGA CellTiter 96® AQ_{ueous} One Solution Reagent cell proliferation assay (Figure 2.7.1.). This method employs the bioreduction of a tetrazolium compound to formazan in order to quantitate cell viability. Cells are first dosed and incubated with potential cytotoxic compounds in 96-well culture plates, and then incubated for 4 h with MTS([3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt,). Dehydrogenase enzymes from active cells utilize either NADPH or NADH to reduce MTS into the formazan byproduct, which can be quantitated at 490 nm by an electronic plate reader. When read against a control, this quantity has been shown to be a direct indication of the number of viable cells.

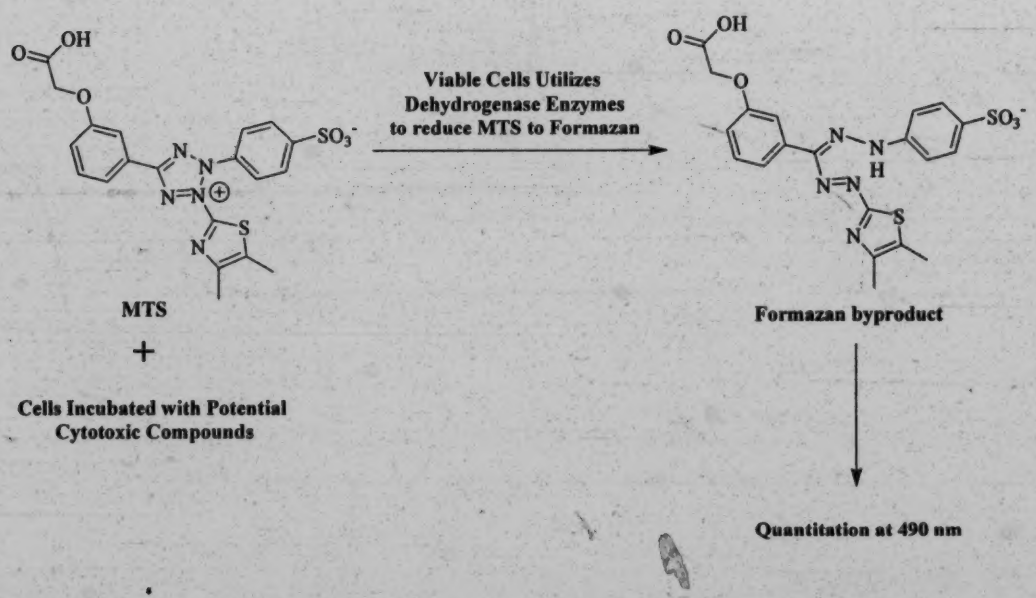


Figure 2.7.1. Schematic of PROMEGA CellTiter 96® AQ_{ueous} One Solution Reagent Cell Proliferation Assay.

The cells were dosed with nine compounds at 100 μM, and the cytotoxicity data are shown below (Chart 2.7.1). These preliminary results suggest that the 1,2,3,4-tetrahydro-naphthyl compounds enhance cell growth. The 1,2,3,4-tetrahydro -anthranyl compounds showed better cytotoxic activity. These results may suggest that the anthranyl compounds could possibly serve as better intercalators into DNA as compared to that of the naphthyl compounds. Variation in the carbohydrate motif from that of the monosaccharide cores found in the natural anthracycline antibiotics (i.e. daunosamine and acosamine sugars) to that of the 4-*O*-benzyl analogs and the tri-deoxy monosaccharide seem to have little influence on cytotoxicity for both series of compounds.

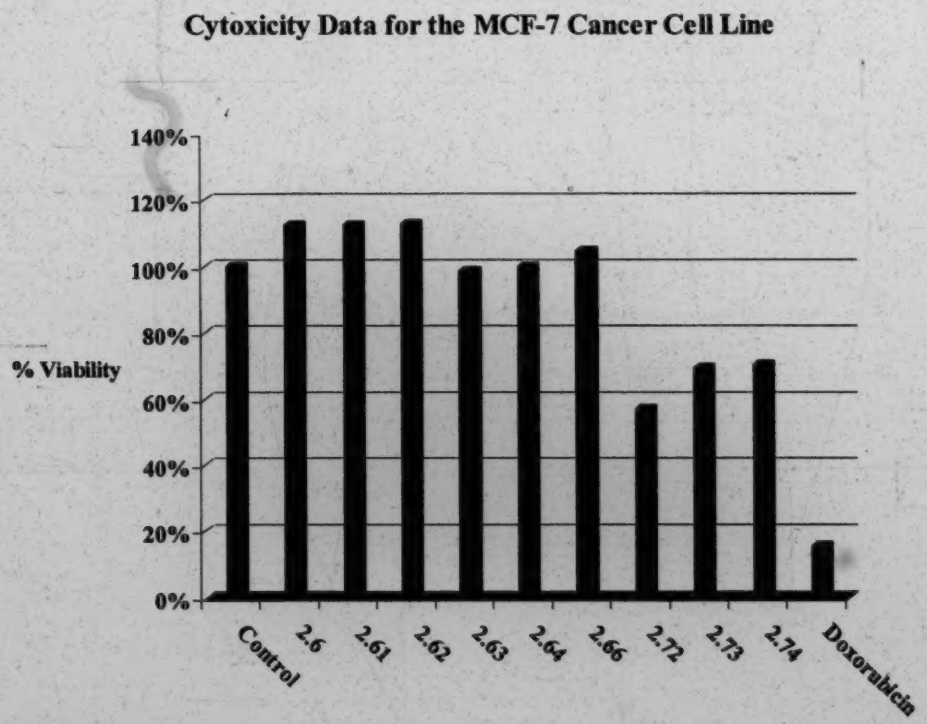


Figure 2.7.2. Cytotoxicity Data for Target compounds dosed at 100 μM.

2.8. Conclusion

In summary, a total of nine anthracycline mimetics were prepared. In these structures, the anthracycline core was replaced with similar analogs containing 1,2,3,4-tetrahydro-naphthyl and 1,2,3,4-tetra-anthranyl ring systems. The 1,2,3,4-tetra-hydro-naphthyl core was prepared from the commercially available anthranilic acid in nine steps with an overall yield of 13%. The 1,2,3,4-tetrahydro-anthranyl core was synthesized from the readily available 1,2,4,5-tetrabromobenzene in 14 steps and after resolution with an overall yield of 4%. The monosaccharide donors were prepared starting from L-rhamonose, via the common intermediate, L-rhamnal. Glycosylation was performed with the use of $AgPF_6$ and DTBMP, which gave the desired α product in most cases. Both the α and the β products were obtained with the use of sugar donor **2.37** and this outcome may arise from a remote participation effect of the acetate group at the C-4 position that can lead to the β isomer. All targets prepared were screened for their biological activity against the MCF-7 cancer cell line. Preliminary results suggest that the 1,2,3,4-tetrahydro-naphthyl compounds enhance cell growth, while the 1,2,3,4-tetrahydro-anthranyl compounds showed better cytotoxic activity. Variations in the carbohydrate cores for both series of compounds showed little influence on overall activity. Future work should therefore include the synthesis of a tetracyclic system (i.e. 1,2,3,4-tetrahydro-tetranyl core), which might promote better intercalation into DNA, similar to that of the anthracycline cores. The addition of other functionalities to the aglycone (i.e. $-OCH_3$, and CF_3) at various positions on the aromatic ring system may also promote better activity. Changing of the monosaccharide residue to either a di- or a trisaccharide system should also be examined.

CHAPTER 3

EXPERIMENTAL PROCEDURES

3.1. General Methods.

All reagents used were purchased from commercial sources and were used without further purification unless noted. Solvents used in reactions were purified using a PURESOLV-400 System from Innovative Technology Inc. Unless stated otherwise, all reactions were carried out under a positive pressure of argon and were monitored by TLC on silica gel G-25 UV_{254} (0.25 mm, Macherey-Nagel). Spots were detected under UV light and/or by charring with 10% H_2SO_4 in ethanol, or in acidified ethanolic anisaldehyde. Solvents were evaporated under reduced pressure and below 50 °C (water bath). Column chromatography was performed on silica gel 60 (40-60 mM). The ratio between silica gel and crude product ranged from 100:1 to 20:1 (w/w). Melting points were recorded on an eletrothermal melting point apparatus. ^1H NMR spectra were recorded on VARIAN INOVA-NMR spectrometers at 300, 400, 500 or 600 MHz, and chemical shifts are referenced to either TMS (0.0, $CDCl_3$) or CD_2HOD (4.78, CD_3OD). ^{13}C NMR spectra were recorded at 100 or 125 MHz, and ^{13}C chemical shifts are referenced to $CDCl_3$ (77.23, $CDCl_3$) or CD_3OD (48.9, CD_3OD). ^1H NMR data are reported as though they are first order, and the peak assignments were made by 2D-NMR spectroscopy (^1H-^1H COSY, HMQC and HMBC). ESI-MS spectra were recorded on samples suspended in THF or CH_3OH and added NaCl. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter at the sodium D line (589 nm). Optical rotations are in units of $deg \cdot mL(dm \cdot g)^{-1}$.

General Assignment for the 1,2,3,4-Tetrahydro-naphthyl/anthranyl Aglycone.

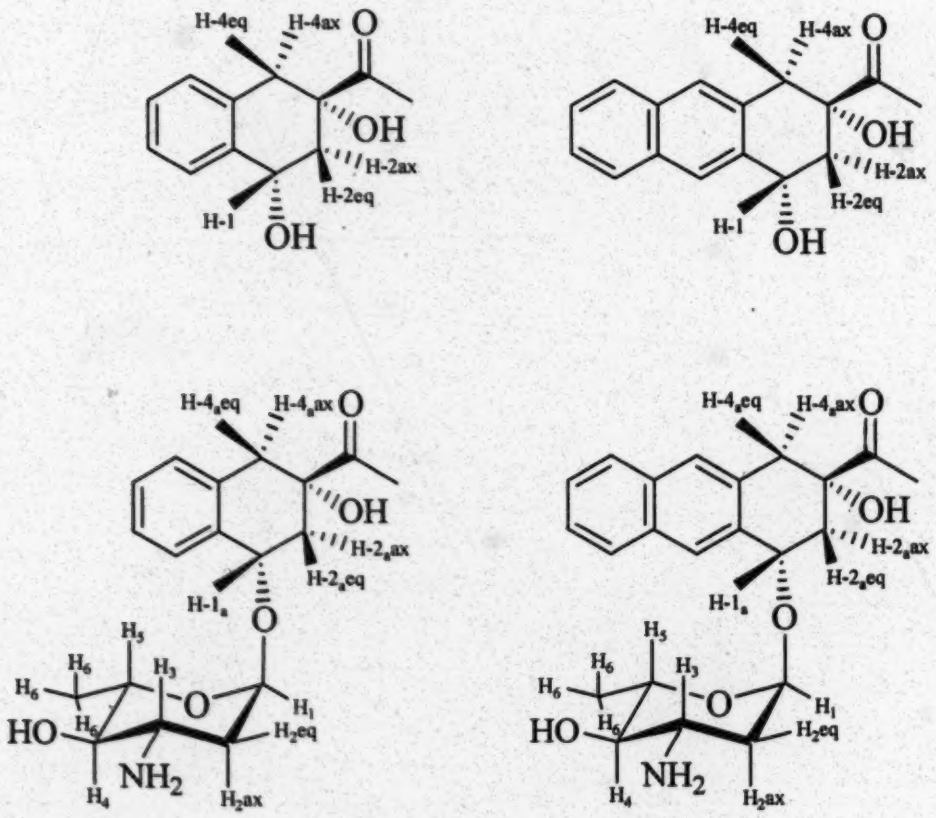


Figure 3.1.1. Structural Assignments of Compounds.

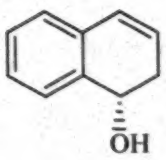
3.1.1. Cytotoxicity assays

We assayed our library of compounds against the breast cancer cell line MCF-7 utilizing the PROMEGA CellTiter 96® AQ_{ueous} One solution reagent pell proliferation assay, which employs the bioreduction of a tetrazolium compound to formazan in order to quantitate cell viability. Cells (~5000/well) were inculbated in the cell culture media (DMEM/High, 10% fetal bovine serum, 1% L-Glutamine, 1% Sodium Pyruvate) in 96-well culture plate for 24 h, and then dosed and incubated with potential cytotoxic compounds in the serum-free media (DMEM-F12, 1mg/mL Human Albumin, 5mg/L Huamn Transferrin, 5mg/L Bovine Insulin) for 48 h. After that, MTS ([3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) solution was added into the wells and the plate was incubated for an additional 4 h. Dehydrogenase enzymes of viable cells reduces the MTS to the formazan byproduct, which can be quantitated at 490 nm by an electronic plate reader. When read against a control, this quantity has been shown to be a direct indication of the number cells of viable.

3.2. Procedures for the Synthesis of 1,2,3,4-Tetrahydro-naphthyl Core

2.14

1,4-Dihydro-1,4-epoxynaphthalene (2.14). Isoamyl nitrite (8.72 g, 74 mmol) in dimethoxyethane (10 mL) and anthranilic acid (6.2 g, 45 mmol) in dimethoxyethane (22 mL) were pre-mixed together and this mixture was added dropwise to a solution of furan (50 mL) and dimethoxyethane (50 mL) at reflux over a period of 90 min. The mixture was further stirred for another 60 min before 10% aq NaOH (30 mL) was added. The mixture was extracted with hexane (3 x 50 mL), and the combined organic layers were washed with a satd aq soln of $NaHCO_3$, water, dried over Na_2SO_4 and concentrated. Sublimation of the residue followed by recrystallization from Et_2O provided **2.14** (3.55 g, 55%) as a white solid: R_f 0.51 (4:1, hexanes-EtOAc); ^1H NMR (300 MHz, $CDCl_3$, δ_H) 7.22-7.29 (m, 2 H, Ar), 7.03-7.05 (m, 2 H, alkene), 6.96-7.00 (m, 2 H, Ar), 5.76 (s, 2 H, -OCH); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 149.0 (2 x Ar), 142.9 (2 x Ar), 125.1 (2 x Ar), 120.4 (2 x alkene), 82.4 (2 x C-O).



2.15

(*S*)-(1H,2H)dihydronaphthalen-1-ol (2.15). To a flame dried flask containing $Ni(COD)_2$ (0.53 g, 1.93 mmol) was added dry THF (30 mL), and the resulting solution was then transferred *via* cannula to a flask containing (*R*)-BINAP (1.86 g, 2.99 mmol). The mixture was stirred for 45 min at which time the solution became a dark burgundy color. The dark solution was then transferred *via* cannula to a flask containing **2.14** (4.0 g, 27.8 mmol) and the mixture was stirred at room temperature for 10 min. DIBAL-H (1.0 M solution in hexanes) was slowly added to the reaction mixture *via* syringe pump over a period of 6 h. Once the addition of DIBAL-H was complete, the reaction was quenched at 0 °C by the addition of a satd aq soln of K_2CO_3 (20 mL) and the mixture was allowed to stir at room temperature for 30 min. The mixture was extracted with EtOAc (3 x 60 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by chromatography (4:1, hexanes-EtOAc) to yield **2.15** (3.24 g, 85%, 98% e.e.) as a white solid: R_f 0.47 (4:1, hexanes-EtOAc); $[\alpha]_D$ -35.8 (*c* 1.4, $CHCl_3$); ^1H NMR (500 MHz, CD_3OD, δ_H) 7.35-7.39 (m, 1 H, Ar), 7.17-7.23 (m, 2 H, Ar), 7.05-7.09 (m, 1 H, Ar), 6.50 (app dt, 1 H, $J_{3,4}$ = 9.6 Hz, $J_{2ax,4} = J_{2eq,4}$ = 1.9 Hz, H-4), 5.96 (app dt, 1 H, $J_{3,4}$ = 9.6 Hz, $J_{3,2ax} = J_{3,2eq}$ 4.3 Hz, H-3), 4.75 (app t, 1 H, $J_{1,2eq} = J_{1,2ax}$ = 6.7 Hz, H-1), 2.53 (dddd, 1 H, $J_{2ax,2eq}$ = 17.5 Hz, $J_{1,2ax}$ = 6.7 Hz, $J_{2ax,3}$ = 4.3 Hz, $J_{2ax,4}$ = 1.9

Hz, H-2ax), 2.44 (dddd, 1 H, $J_{2ax,2eq}$ = 17.5 Hz, $J_{1,2eq}$ = 6.7 Hz, $J_{2eq,3}$ = 4.3 Hz, $J_{2eq,4}$ = 1.9 Hz, H-2eq); ^{13}C NMR (100 MHz, CD_3OD, δ_C) 138.3 (Ar), 134.6 (Ar), 128.9 (Ar), 128.4 (Ar), 128.3 (Ar), 127.4 (Ar), 127.3 (alkene), 126.6 (alkene), 68.5 (C-1), 33.5 (C-2). HRMS (EI) calcd for (M) $C_{10}H_{10}O$: 146.0732, found: 146.0734.

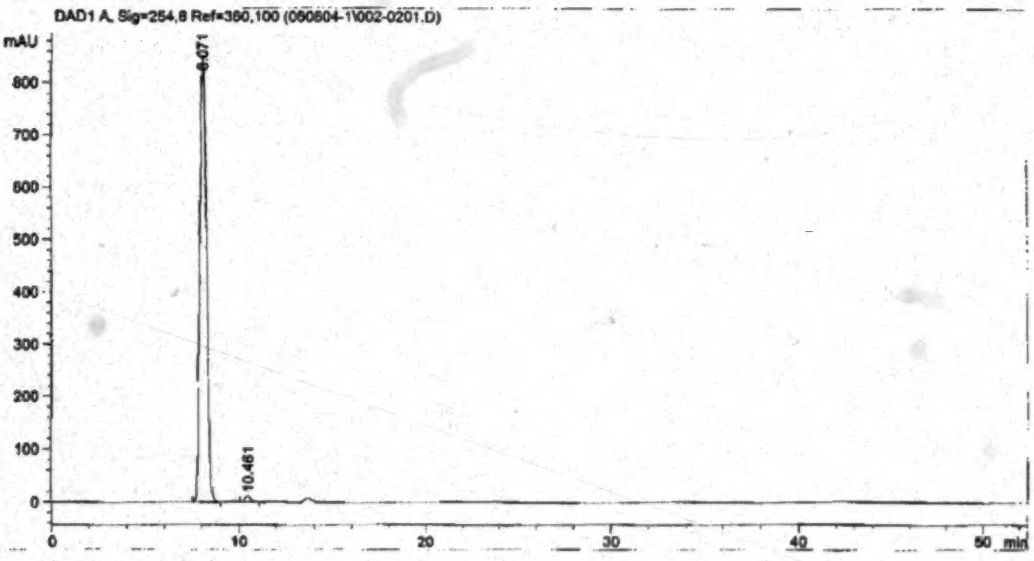
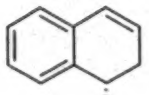
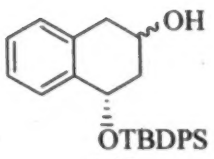


Figure 3.2.1. HPLC Trace of (*S*)-(1H,2H)dihydronaphthalen-1-ol.



2.16

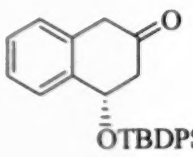
(*S*)-1-*tert*-Butyldiphenylsiloxy-3,4-dihydro-naphthalene (2.16). Alkene **2.15** (3.2 g, 21.9 mmol), imidazole (3.73 g, 54.8 mmol) and DMAP (50 mg, 0.41 mmol) were dissolved in CH_2Cl_2 (50 mL). TBDPSCl (6.02 g, 21.9 mmol) was added to the solution, and the reaction mixture was stirred for 4 h. Once the reaction was complete, the mixture was concentrated and the residue was purified by chromatography (hexanes) to yield **2.16** (7.16 g, 85%) as a clear oil: R_f 0.56 (hexanes); $[\alpha]_D$ -40.2 (*c* 1.4, C_6H_6); ^{1}H NMR (300 MHz, C_6D_6, δ_H) 7.67-7.84 (m, 4 H, Ar), 7.52-7.55 (m, 1 H, Ar), 7.06-7.26 (m, 8 H, Ar), 6.89-6.93 (m, 1 H, Ar), 6.32 (br d, 1 H, $J_{4,3}$ = 9.6 Hz, H-4), 5.60 (ddd, 1 H, $J_{3,4}$ = 9.6 Hz, $J_{2ax,3}$ = 4.5 Hz, $J_{2eq,3}$ = 4.3 Hz, H-3), 5.05 (dd, 1 H, $J_{1,2eq}$ = 7.1 Hz, $J_{1,2ax}$ = 6.9 Hz, H-1), 2.41 (dddd, 1 H, $J_{2eq,2ax}$ = 16.9 Hz, $J_{1,2eq}$ = 7.1 Hz, $J_{2eq,3}$ = 4.3 Hz, $J_{2eq,4}$ = 1.8 Hz, H-2eq), 2.09 (dddd, 1 H, $J_{2ax,2eq}$ = 16.9 Hz, $J_{1,2ax}$ = 6.9 Hz, $J_{2ax,3}$ = 4.5 Hz, $J_{2ax,4}$ = 1.8 Hz, H-2ax), 1.16 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, C_6D_6, δ_C) 137.8 (Ar), 136.3 (3 x Ar), 136.2 (3 x Ar), 135.0 (Ar), 134.2 (Ar), 133.9 (Ar), 130.1 (Ar), 130.0 (Ar), 128.0 (2 x Ar), 127.9 (2 x Ar), 127.5 (C-4), 126.5 (Ar), 126.3 (C-3), 125.9 (Ar), 70.4 (C-1), 33.3 (C-2), 27.3 ($C(CH_3)_3$), 19.8 ($C(CH_3)_3$). HRMS (ESI) calcd for (M+Na) $C_{26}H_{28}OSiNa$: 407.1807, found: 407.1810.



2.17

(*S*)-1-*tert*-Butyldiphenylsiloxy-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (2.17). Compound **2.16** (7.10 g, 18.5 mmol) was dissolved in CH_2Cl_2 (50 mL) and the resulting solution was added to DMDO (ca. 0.05-0.08 M solution in acetone, 400 mL). The reaction mixture was stirred for 2 h at 0 °C, and concentrated. The crude product was used without any further purification; R_f 0.52 (15:1, hexanes-EtOAc). The epoxide (7.41 g, 18.5 mmol) was then dissolved in Et_2O (60 mL) and the mixture was cooled to 0 °C. $LiAlH_4$ (1.20 g, 31.5 mmol) was added to the mixture, and the solution was stirred for 70 min at room temperature Excess EtOAc was added to quench the residual $LiAlH_4$, followed by 4 M NaOH (3 mL). The mixture was filtered through Celite and concentrated. The crude product was purified by chromatography (5:1, hexanes-EtOAc) to yield **2.17** as a 95:5 mixture of isomers, which were inseparable (5.95 g, 80% over 2 steps) as a clear oil. Data for the major isomer: R_f 0.32 (5:1, hexanes-EtOAc); $[\alpha]_D$ -45.8 (*c* 1.3, $CHCl_3$); ^{1}H NMR (600 MHz, CD_3OD, δ_H) 6.80-7.78 (m, 14 H, Ar), 4.94 (app t, 1 H, $J_{1,2ax} = J_{1,2eq}$ = 5.3 Hz, H-1), 4.47-4.51 (m, 1 H, H-3), 3.17 (dd, 1 H, $J_{4ax,4eq}$ = 16.2 Hz $J_{4ax,3}$ = 7.5 Hz, H-4ax), 2.58 (dd, 1 H, $J_{4eq,4ax}$ = 16.2 Hz, $J_{4eq,3}$ = 7.5 Hz, H-4eq), 2.23 (ddd, 1 H, $J_{2ax,2eq}$ = 12.8 Hz, $J_{1,2ax}$ = 5.3 Hz, $J_{2ax,3}$ = 3.8 Hz, H-2ax), 1.67 (ddd, 1 H, $J_{2ax,2eq}$ = 12.8 Hz, $J_{1,2eq}$ = 5.3 Hz, $J_{2eq,3}$ = 3.8 Hz, H-2eq), 1.05 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, C_6D_6, δ_C)

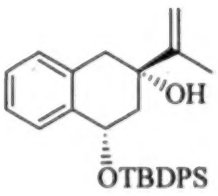
138.6 (Ar), 137.1 (4 x Ar), 136.1 (Ar), 135.2 (Ar), 135.1 (Ar), 131.0 (Ar), 130.8 (Ar), 130.4 (Ar), 130.1 (Ar), 128.9 (2 x Ar), 128.8 (Ar), 128.6 (2 x Ar), 126.8 (Ar), 71.7 (C-1), 64.8 (C-3), 41.9 (C-4), 39.5 (C-2), 27.6 ($C(CH_3)_3$), 20.2 ($C(CH_3)_3$). HRMS (ESI) calcd for (M+Na) $C_{26}H_{30}O_2SiNa$: 425.1913, found: 425.1907. Anal. Calcd. for: C, 77.57; H, 7.51. Found: C, 77.84; H, 7.34.



2.18

(*S*)-1-*tert*-Butyldiphenylsiloxy-1,2,3,4-tetrahydronaphtha-3-one (2.18). Alcohol **2.17** (5.0 g, 12.5 mmol) was dissolved in EtOAc (40 mL) and IBX (8.75 g, 31.3 mmol) was added. The resulting mixture was stirred for 6 h at 85 °C, whereupon the cloudy solution changed from colorless to light yellow. The suspension was filtered, and concentrated, and the crude product was purified by chromatography (20:1, hexanes-EtOAc) to yield **2.18** (4.5 g, 90%) as a white solid: R_f 0.70 (5:1, hexanes-EtOAc); $[\alpha]_D$ -64.8 (*c* 1.3, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6, δ_H) 7.67-7.78 (m, 2 H, Ar), 7.36-7.49 (m, 6 H, Ar), 7.23-7.32 (m, 3 H, Ar), 7.08-7.19 (m, 2 H, Ar), 6.90 (d, 1 H, J = 7.4 Hz, Ar), 4.82 (dd, 1 H, $J_{1,2ax}$ = 4.5 Hz, $J_{1,2eq}$ = 3.2 Hz, H-1), 3.76 (d, 1 H, $J_{4ax,4eq}$ = 19.9 Hz, H-4ax), 3.22 (d, 1 H, $J_{4ax,4eq}$ = 19.9 Hz, H-4eq), 2.67 (dd, 1 H, $J_{2ax,2eq}$ = 16.5 Hz, $J_{1,2ax}$ = 4.5 Hz, H-2ax), 2.09 (dd, 1 H, $J_{2ax,2eq}$ = 16.5 Hz, $J_{1,2eq}$ = 3.2 Hz, H-2eq),

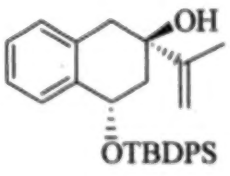
1.03 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, C_6D_6, δ_C) 205.5 (C-3), 138.5 (Ar), 136.3 (4 x Ar), 135.3 (Ar), 134.2 (Ar), 133.9 (Ar), 133.7 (Ar), 130.3 (Ar), 130.1 (Ar), 128.9 (Ar), 128.3 (2 x Ar), 127.9 (2 x Ar), 127.3 (Ar), 126.5 (Ar), 71.5 (C-1), 47.4 (C-4), 44.2 (C-2), 27.1 ($C(CH_3)_3$), 19.5 ($C(CH_3)_3$). HRMS (ESI) calcd for (M+Na) $C_{26}H_{28}O_2SiNa$: 423.1756, found: 423.1751.



2.19

(1*S*,3*S*)-1-*tert*-Butyldiphenylsiloxy-3-hydroxyl-3-isopropenyl-1,2,3,4-tetrahydro-naphthalene (2.19). Cerium chloride heptahydrate (4.53 g, 18.4 mmol) and a magnetic stir bar were placed in a flask and heated to 140–142 °C in vacuo (0.1 Torr) for 24 h. The flask was cooled to rt, and ketone **2.18** (2.10 g, 5.25 mmol) and THF (20 mL) were added. The reaction mixture was vigourously stirred for 1.5 h after when the mixture had become an orange paste. Isopropenylmagnesium bromide 0.5 M in THF (18.9 mL, 9.45 mmol) was added over 10 min at 0 °C and the solution was stirred for 4 h. The mixture was then treated with a satd aq soln of NH_4Cl (50 mL), and EtOAc (50 mL) was added. The mixture was filtered through Celite and the aq layer was extracted with EtOAc (2 x 40 mL). The combined organic layers were dried over Na_2SO_4 and purified

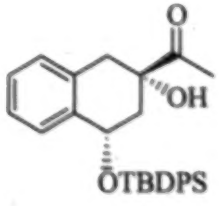
by chromatography (15:1, hexanes-EtOAc) to yield **2.19** (1.86 g, 67%) as a white solid. The solid was recrystallized from hexane/Et_2O (1:1) (m.p.: 95-98 °C): R_f 0.65 (5:1, hexanes-EtOAc); $[\alpha]_D$ -10.5 (*c* 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 6.92-7.82 (m, 14 H, Ar), 5.08 (s, 1 H, alkene), 4.94 (app t, 1 H, $J_{1,2ax} = J_{1,2eq} = 3.8$ Hz, H-1), 4.87 (br s, 1 H, alkene), 4.59 (s, 1 H, 3°-OH), 3.08 (br d, 1 H, $J_{4ax,4eq} = 16.8$ Hz, H-4ax), 3.03 (d, 1 H, $J_{4ax,4eq} = 16.8$ Hz, H-4eq) 2.30 (ddd, 1 H, $J_{2ax,2eq} = 14.0$ Hz, $J_{1,2eq} = 3.8$ Hz, $J_{2eq,4} = 1.3$ Hz, H-2eq), 2.00 (dd, 1 H, $J_{2ax,2eq} = 14.0$ Hz, $J_{1,2ax} = 3.8$ Hz, H-2ax), 1.82 (s, 3 H, $=CCH_3$), 1.03 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 149.9 (alkene), 136.2 (2 x Ar), 135.8 (2 x Ar), 135.2 (Ar), 134.8 (Ar), 134.6 (Ar), 133.0 (Ar), 132.9 (Ar), 130.1 (Ar), 129.8 (Ar), 129.6 (Ar), 129.5 (Ar), 128.1 (Ar), 127.9 (Ar), 127.7 (Ar), 127.6 (Ar), 125.8 (Ar), 110.0 (alkene), 73.1 (C-3), 70.6 (C-1), 41.6 (C-4), 40.5 (C-2), 26.9 ($=CCH_3$), 19.3 ($C(CH_3)_3$), 18.7 ($C(CH_3)_3$). HRMS (ESI) calcd for (M+Na) $C_{29}H_{34}O_2SiNa$: 465.2226, found: 465.2221. Anal. Calcd. for: C, 78.68; H, 7.74. Found: C, 78.35; H, 7.68.



2.19a

(1*R*,3*S*)-1-*tert*-Butyldiphenylsiloxy-3-hydroxyl-3-isopropenyl-1,2,3,4-tetrahydro-naphthalene (2.19a). Product **2.19a** (0.278 g, 13%) was obtained as a clear oil: R_f 0.62 (5:1, hexanes-EtOAc): $[\alpha]_D$ +15.5 (*c* 0.5, $CHCl_3$) ^1H NMR (400 MHz, $CDCl_3$, δ_H)

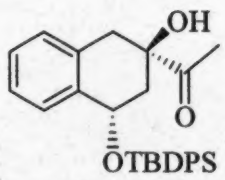
7.03-7.82 (m, 14 H, Ar), 5.22 (dd, 1 H, $J_{1,2ax}$ = 9.7 Hz, $J_{1,2eq}$ = 5.8 Hz, H-1), 4.93 (s, 1, alkene), 4.77 (br s, 1 H, alkene), 3.10 (d, 1 H, $J_{4ax,4eq}$ = 16.8 Hz, H-4ax), 2.68 (d, 1 H, $J_{4ax,4eq}$ = 16.8 Hz, H-4eq) 1.87-2.00 (m, 2 H, H-2ax, H-2eq), 1.72 (s, 3 H, $=CCH_3$), 1.03 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 150.9 (alkene), 136.2 (2 x Ar), 135.9 (2 x Ar), 135.2 (Ar), 134.8 (Ar), 134.6 (Ar), 133.0 (Ar), 132.9 (Ar), 130.1 (Ar), 129.8 (Ar), 129.6 (Ar), 129.5 (Ar), 128.1 (Ar), 127.9 (Ar), 127.7 (Ar), 127.6 (Ar), 125.8 (Ar), 109.4 (alkene), 74.5 (C-3), 69.4 (C-1), 42.7 (C-4), 40.4 (C-2), 26.6 ($=CCH_3$), 19.5 ($C(CH_3)_3$), 18.7 ($C(CH_3)_3$). HRMS (ESI) calcd for (M+Na) $C_{29}H_{34}O_2SiNa$: 465.2226, found: 465.2219.



2.20

(1*S*,3*S*)-1-*tert*-butyldiphenylsiloxy-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (2.20). Alkene **2.19** (0.97 g, 2.19 mmol) was dissolved in CH_2Cl_2 and placed in a 3-neck flask. The mixture was cooled to -78 °C, and ozone was bubbled through the solution for 5 min. Triethylamine (5.74 g, 21.9 mmol) was added and the reaction mixture was further stirred for 24 h. The mixture was concentrated and purified by chromatography (20:1, hexanes-EtOAc) to yield **2.20** (0.73 g, 75%) as an oil: R_f 0.53

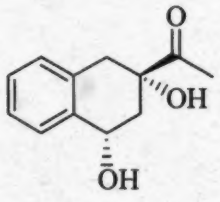
(5:1, hexanes-EtOAc); $[\alpha]_D$ -29.7 (*c* 0.7, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, δ_H) 6.80-7.80 (m, 14 H, Ar), 5.25 (s, 1 H, -OH), 4.96 (app t, 1 H, $J_{1,2ax} = J_{1,2eq} = 3.8$ Hz, H-1), 3.12 (br d, 1 H, $J_{4ax,4eq} = 16.7$ Hz, H-4ax), 3.01 (d, 1 H, $J_{4ax,4eq} = 16.7$ Hz, H-4eq), 2.35 (s, 3 H, $C(O)CH_3$), 2.24 (ddd, 1 H, $J_{2ax,2eq} = 14.3$ Hz, $J_{1,2eq} = 3.8$ Hz, $J_{2eq,4eq} = 2.0$ Hz, H-2eq), 2.01 (dd, 1 H, $J_{2ax,2eq} = 14.3$ Hz, $J_{1,2ax} = 3.8$ Hz, H-2ax), 1.03 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 212.6 (C=O), 136.1 (4 x Ar), 135.3 (Ar), 134.8 (Ar), 133.1 (Ar), 132.6 (Ar), 132.5 (Ar), 130.2 (Ar), 129.9 (Ar), 129.6 (Ar), 129.5 (Ar), 129.4 (Ar), 128.0 (Ar), 127.7 (Ar), 127.6 (Ar), 126.1 (Ar), 78.5 (C-3), 70.0 (C-1), 38.9 (C-4), 37.6 (C-2), 26.9 ($C(O)CH_3$), 24.7 ($C(CH_3)_3$), 19.3 ($C(CH_3)_3$). HRMS (ESI) calcd for (M+Na) $C_{28}H_{32}O_3SiNa$: 467.2018, found: 465.2013.



2.20a

(1*R*,3*S*)-1-*tert*-Butyldiphenylsiloxy-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (2.20a). Reaction of **2.19a**, as described for **2.19**, provided **2.20a** (0.150 g, 67%) as an oil: R_f 0.56 (5:1, hexanes-EtOAc); $[\alpha]_D$ +35.6 (*c* 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 7.08-7.78 (m, 14 H, Ar), 5.25 (dd, 1, $J_{1,2ax} = 9.5$ Hz, $J_{1,2eq} = 5.3$ Hz, H-1), 3.67 (s, 1 H, 3°-OH), 3.22 (d, 1 H, $J_{4ax,4eq} = 16.4$ Hz, H-4ax), 2.67 (d, 1 H, $J_{4ax,4eq} =$

16.4 Hz, H-4eq), 2.13 (s, 3 H, C(O)CH_3), 2.01-2.09 (dd, 1 H, $J_{2ax,2eq}$ = 12.9 Hz, $J_{1,2ax}$ = 9.5 Hz, H-2ax), 1.84 (ddd, 1 H, $J_{2ax,2eq}$ = 12.9 Hz, $J_{1,2eq}$ = 5.3 Hz, $J_{2eq,4eq}$ = 1.5 Hz, H-2eq), 1.17 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 210.3 (C=O), 139.5 (Ar), 135.9 (4 x Ar), 135.8 (Ar), 134.2 (Ar), 133.5 (Ar), 133.4 (Ar), 132.7 (Ar), 129.8 (2 x Ar), 128.3 (Ar), 127.6 (Ar), 127.5 (Ar), 127.2 (Ar), 126.5 (Ar), 126.1 (Ar), 77.9 (C-3), 68.5 (C-1), 41.3 (C-4), 37.8 (C-2), 27.1 (C(O)CH_3), 23.5 ($C(CH_3)_3$), 19.4 ($C(CH_3)_3$). HRMS (ESI) calcd for (M+Na) $C_{28}H_{32}O_3SiNa$: 467.2018, found: 467.2015.

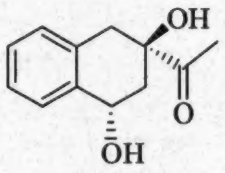


2.11

(1*S*,3*S*)-1-Hydroxy-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (2.11).

Ketone **2.20** (0.73 g, 1.64 mmol) was dissolved in THF (5 mL) and tetrabutylammonium fluoride in 1.0 M THF (1.49 g, 1.65 mmol) was added to the solution. The reaction mixture was stirred for 48 h, concentrated and purified by chromatography (5:1, hexanes-EtOAc) to yield **2.11** (0.254 g, 75%) as an oil: R_f 0.48 (1:1, hexanes-EtOAc); $[\alpha]_D$ +21.1 (*c* 0.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.46-7.48 (m, 1 H, Ar), 7.26-7.31 (m, 2 H, Ar), 7.11-7.14 (m, 1 H, Ar), 4.90 (br s, 1 H, H-1), 4.47 (s, 1 H, 3°-OH), 3.72 (br d, 1 H, *J* = 8.9 Hz, 2°-OH), 3.24 (d, 1 H, $J_{4ax,4eq}$ = 16.5 Hz, H-4ax), 2.84 (dd, 1 H,

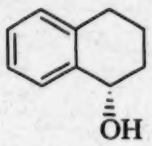
$J_{4ax,4eq}$ = 16.5 Hz, $J_{2eq,4eq}$ = 2.1 Hz, H-4eq), 2.38 (s, 3 H, C(O)CH_3), 2.31 (dd, 1 H, $J_{2ax,2eq}$ = 14.0 Hz, $J_{1,2ax}$ = 4.6 Hz, H-2ax), 2.23 (app dt, 1 H, $J_{2ax,2eq}$ = 14.0 Hz, $J_{1,2eq}$ = 4.6 Hz, H-2eq); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 210.9 (C=O), 136.9 (Ar), 131.5 (Ar), 130.2 (Ar), 129.4 (Ar), 128.4 (Ar), 127.1 (Ar), 78.5 (C-3), 67.1 (C-1), 38.2 (C-4), 36.9 (C-2), 24.0 (C(O)CH_3). HRMS (ESI) calcd for (M+Na) $C_{12}H_{14}O_3Na$: 229.0841, found: 229.0835.



2.11a

(1*S*,3*R*)-1-Hydroxy-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (2.11a).

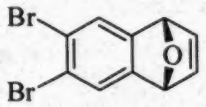
Reaction of **2.20a**, as described for **2.20**, provided **2.11a** (0.050 g, 70%) as an oil: R_f 0.45 (1:1, hexanes-EtOAc); $[\alpha]_D$ -40.2 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 7.00-7.58 (m, 4 H, Ar), 5.05 (br s, 1 H, 3°-OH), 4.78 (br s, 1 H, H-1), 3.72 (br d, 1 H, *J* = 8.9 Hz, 2°-OH), 3.10-3.28 (m, 2 H, H-4ax, H-4eq), 2.43 (s, 3 H, C(O)CH_3), 2.10-2.18 (m, 1 H, H-2ax), 1.96-2.05 (m, 1 H, H-2eq); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 210.6 (C=O), 138.4 (Ar), 128.8 (Ar), 130.2 (Ar), 128.7 (Ar), 127.6 (Ar), 126.3 (Ar), 78.2 (C-3), 66.6 (C-1), 40.4 (C-4), 37.9 (C-2), 23.6 (C(O)CH_3). HRMS (ESI) calcd for (M+Na) $C_{12}H_{14}O_3Na$: 229.0841, found: 229.0836.



2.21

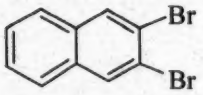
(*S*)-1,2,3,4-Tetrahydro-1-naphthol (2.21). Alkene **2.15** (100 mg, 0.685 mmol) was dissolved in EtOH (5 mL) and 10% Pd/C (20 mg) was added. The reaction mixture was stirred under an atmosphere of H_2 for 24 h. Once the starting material was fully consumed as verified by TLC, the mixture was filtered through Celite and concentrated. The crude product was purified by chromatography (7:1, hexanes-EtOAc) to yield **2.21** (0.071 g, 70%) as a white solid: R_f 0.56 (5:1, hexanes-EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 7.06-7.44 (m, 4 H, Ar), 4.55 (t, 1 H, $J_{1,2ax} = J_{1,2eq} = 5.0$ Hz, H-1), 2.65-2.86 (m, 2 H, H-4ax, H-4eq), 1.62-2.12 (m, 4 H, H-2ax, H-2eq, H-3ax, H-3eq); ^{13}C NMR (100MHz, C_6D_6, δ_C) 138.9 (Ar), 137.0 (Ar), 128.9 (Ar), 128.5 (Ar), 127.4 (Ar), 126.1 (Ar), 68.0 (C-1), 32.2 (C-4), 29.1 (C-2), 18.7 (C-3). HRMS (EI) calcd for (M) $C_{10}H_{12}O$: 148.0888, found: 148.0885.

3.3. Procedures for the Synthesis of 1,2,3,4-Tetrahydro-anthranyl Core



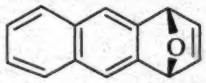
2.25

1,4-Dihydro-1,4-epoxy-2,3-dibromonaphthalene (2.25). 2,3,5,6-Tetrabromobenzene (8.0 g, 20 mmol) was dissolved in toluene (200 mL) and furan (12 mL) was added. The reaction mixture was cooled to -20 °C (dry ice-CH_3CN bath) and *n*-BuLi (12.5 mL, 22 mmol) was added via a syringe pump over 3.5 h. The reaction was quenched by the addition of CH_3OH (1 mL), and washed with water and brine. The combined organic layers were dried over Na_2SO_4 and concentrated to give a yellow oil. The oil was triturated with hexane (100 mL) and concentrated to give a yellow solid. The crude product was recrystallized from CH_3OH (50 mL) to yield **2.25** (4.30 g, 70%) as a white solid: R_f 0.5 (4:1, hexanes-EtOAc); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 7.42 (s, 2 H, Ar), 6.98 (s, 2 H, alkene), 5.76 (s, 2 H, -OCH); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 150.0 (2 x Ar), 142.6 (2 x Ar), 125.4 (2 x alkene-C), 120.6 (2 x Ar), 81.7 (2 x C-O). HRMS (EI) calcd for (M+H) $C_{10}H_7OBr_2$: 301.8864, found: 301.8867.



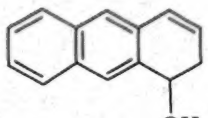
2.24

2,3-Dibromonaphthalene (2.24). Zinc dust (4.0 g, 61.2 mmol) was added to THF (100 mL) and the suspension was cooled to 0 °C. $TiCl_4$ (4 mL, 36.5 mmol) was added slowly under argon into the suspension. After the mixture was heated at reflux for 15 min, **2.25** (2.0 g, 6.58 mmol) in THF (20 mL), was added, and reflux was maintained for 24 h. The reaction mixture was cooled to 0 °C, and HCl (20 mL, 1 M) was added, upon which evolution of gas was observed. The mixture was extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated to give **2.24** (1.50 g, 80%) as a white solid. R_f 0.58 (4:1, hexanes-EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 8.16 (s, 1 H, Ar), 7.96 (s, 1 H, Ar), 7.72-7.77 (m, 2 H, Ar), 7.49-7.54 (m, 2 H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 144.0 (2 x Ar), 141.6 (2 x Ar), 131.8 (2 x Ar), 126.0 (2 x Ar), 118.6 (2 x Ar). HRMS (EI) calcd for (M+H) $C_{10}H_7Br_2$: 284.8914, found: 284.8916.



2.22

1,4-Epoxy-1,4-dihydroanthracene (2.22). To a stirred solution of **2.24** (3.0 g, 0.011 mol) and furan (32 mL, 0.43 mol) in dry THF (20 mL) at 0 °C was added dropwise PhLi (1.5 M solution in cyclohexane/ether; 8.0 mL, 0.012 mol). The purple mixture was stirred at room temperature for 1.5 h, concentrated, and purified by column chromatography (10:1, hexanes-EtOAc) to yield **2.22** (1.43 g, 70%) as a yellow solid. R_f 0.50 (4:1, hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.70-7.74 (m, 2 H, Ar), 7.6 (s, 2 H, Ar), 7.42-7.46 (m, 2 H, Ar), 6.75-6.82 (m, 2 H, alkene), 5.78-5.82 (m, 2 H, allyl); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 144.1 (2 x Ar), 141.7 (2 x Ar), 131.9 (2 x Ar), 128.1 (2 x Ar), 126.1 (2 x Ar), 118.6 (2 x alkene), 81.8 (2 x OCH). HRMS (EI) calcd for (M) $C_{14}H_{10}O$: 194.0732, found: 194.0735.



2.26

1-Hydroxy-3,4-dihydro-anthracene (2.26). To a flame dried flask containing $Ni(COD)_2$ (0.065 g, 0.237 mmol) was added dry THF (15 mL), and the resulting solution was then transferred *via* cannula to a flask containing (*R*)-BINAP (0.232 g, 0.373 mmol). The mixture was stirred for 45 min at which point the solution became a dark burgundy color. The dark solution was then transferred *via* cannula to a flask containing **2.22** (0.657 g, 3.39 mmol) and the mixture was stirred at room temperature for 10 min. DIBAL-H (1.0 M solution in hexanes) was slowly added to the mixture *via* syringe pump over a period of 3 h. Once the addition of DIBAL-H was complete, the reaction was quenched at 0 °C by the addition of a satd aq soln of K_2CO_3 (20 mL) and the mixture was allowed to stir at room temperature for 30 min. The mixture was extracted with EtOAc (3 x 50 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by chromatography (4:1, hexanes-EtOAc) to yield **2.26** (0.425 g, 64%, 55% e.e.) as a white solid: R_f 0.46 (4:1, hexanes-EtOAc); IR υ_{max} cm^{-1}: 3337 (s); ^1H NMR (500 MHz, CD_3OD, δ_H) 7.82 (s, 1 H, Ar), 7.72-7.79 (m, 2 H, Ar), 7.47 (s, 1 H, Ar), 7.34-7.40 (m, 2 H, Ar), 6.65 (br d, 1 H, $J_{3,4}$ = 9.1 Hz, H-4), 6.10 (app dt, 1 H, $J_{3,4}$ = 9.1 Hz, $J_{3,2ax}$ = $J_{3,2eq}$ = 4.3 Hz, H-3), 4.75 (app t, 1 H, $J_{1,2ax}$ = $J_{1,2eq}$ = 7.2 Hz, H-1), 2.58 (dddd, 1 H, $J_{2ax,2eq}$ = 17.1 Hz, $J_{1,2ax}$ = 7.2 Hz, $J_{2ax,3}$ = 4.3 Hz, $J_{2ax,4}$ =

1.8 Hz, H-2ax), 2.47 (dddd, 1 H, $J_{2ax,2eq}$ = 17.1 Hz, $J_{1,2eq}$ = 7.2 Hz, $J_{2eq,3}$ = 4.3 Hz, $J_{2eq,4}$ = 1.8 Hz, H-2eq); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 137.6 (Ar), 134.8 (Ar), 134.6 (Ar), 133.1 (Ar), 128.8 (2 x Ar), 128.7 (Ar), 127.5 (Ar), 127.0 (Ar), 126.7 (Ar), 125.6 (2 x alkene), 68.9 (C-1), 33.8 (C-2). HRMS (ESI) calcd for (M+Na) $C_{14}H_{12}ONa$: 219.0786, found: 219.0780.

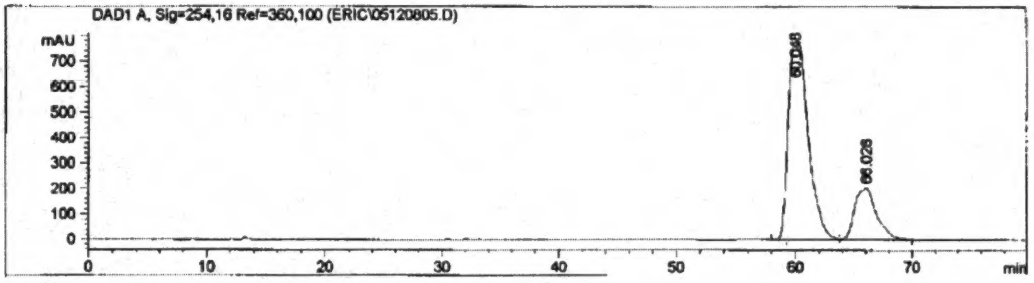
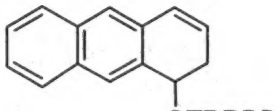


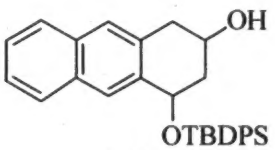
Figure 3.3.1. HPLC Trace for 1-Hydroxy-3,4-dihydro-anthracene.



2.27

1-*tert*-Butyldiphenylsiloxy-3,4-dihydro-anthracene (2.27). Alkene **2.26** (0.162 g, 0.826 mmol), imidazole (0.139 g, 2.04 mmol) and catalytic amount of DMAP were dissolved in CH_2Cl_2 (10 mL). TBDPSCl (0.227 g, 0.826 mmol) was added to the solution, and the reaction mixture was stirred for 3 h. Once the reaction was complete, the mixture was

concentrated and the residue was purified by chromatography (hexanes) to yield **2.27** (0.300 g, 86%) as a clear oil: R_f 0.18 (hexanes); ^{1}H NMR (500 MHz, C_6D_6, δ_H) 7.08-7.90 (m, 16 H, Ar), 6.49 (br d, 1 H, $J_{4,3}$ = 11.6 Hz, H-4), 5.68 (ddd, 1 H, $J_{3,4}$ = 11.6 Hz, $J_{2ax,3}$ = $J_{2eq,3}$ = 3.9 Hz, H-3), 5.21 (dd, 1 H, $J_{1,2ax}$ = 8.7 Hz, $J_{1,2eq}$= 5.6 Hz, H-1), 2.51 (dddd, 1 H, $J_{2ax,2eq}$ = 16.7 Hz, $J_{1,2ax}$ = 8.7 Hz, $J_{2ax,3}$ = 3.9 Hz, $J_{2ax,4}$ = 2.1 Hz, H-2ax), 2.19-2.25 (m, 1 H, H-2eq), 1.20 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, C_6D_6, δ_C) 136.7 (Ar), 136.3 (4 x Ar), 136.2 (4 x Ar), 135.0 (Ar), 134.2 (Ar), 133.9 (Ar), 133.6 (Ar), 132.5 (Ar), 130.1 (Ar), 130.0 (Ar), 128.4 (Ar), 128.0 (2 x Ar), 126.6 (Ar), 126.2 (Ar), 125.9 (Ar), 125.3 (alkene), 125.0 (alkene), 70.7 (C-1), 33.6 (C-2), 27.3 ($C(CH_3)_3$), 19.8 ($C(CH_3)_3$). HRMS (ESI) calcd for (M+Na) $C_{30}H_{30}OSiNa$: 457.1964, found: 457.1958.

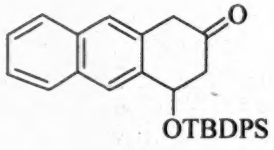


2.28

1-*tert*-Butyldiphenylsiloxy-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (2.28).

Alkene **2.27** (0.691 g, 1.59 mmol) was added to DMDO (ca. 0.05 M solution in acetone, 22 mL), and the solution was stirred for 5 h at room temperature, and then concentrated. The crude product was used without any further purification. The epoxide (0.632 g, 1.40 mmol) was then dissolved in Et_2O (15 mL), and $LiAlH_4$ (0.10 g, 2.66 mmol) was added to the mixture. The reaction mixture was stirred for 1.5 h at room temperature. Excess

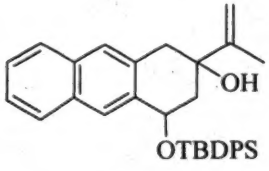
EtOAc was added to quench the residual $LiAlH_4$ followed by 3 M NaOH (2 mL). The reaction mixture was filtered through Celite and concentrated. The crude product was purified by chromatography (8:1, hexanes-EtOAc) to yield **2.28** as a single isomer (0.44 g, 63%) as a white solid: R_f 0.43 (5:1, hexanes-EtOAc); IR υ_{max} cm^{-1}: 3326 (s); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.25-7.80 (m, 16 H, Ar), 5.18 (app t, 1 H, $J_{1,2ax} = J_{1,2eq} = 4.9$ Hz, H-1), 4.56-4.65 (m, 1 H, H-3), 3.45 (dd, 1 H, $J_{4ax,4eq} = 15.8$ Hz, $J_{3,4ax} = 6.9$ Hz, H-4ax), 2.83 (dd, 1 H, $J_{4ax,4eq} = 15.8$ Hz, $J_{3,4eq} = 6.9$ Hz, H-4eq), 2.30 (ddd, 1 H, $J_{2ax,2eq} = 17.7$ Hz, $J_{2ax,3} = 10.9$ Hz, $J_{1,2ax} = 4.9$ Hz, H-2ax), 1.81 (ddd, 1 H, $J_{2ax,2eq} = 17.7$ Hz, $J_{2eq,3} = 10.9$ Hz, $J_{1,2eq} = 4.9$ Hz, H-2eq), 1.44 (br s, 1 H, 2°-OH), 1.06 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 136.6 (Ar), 136.0 (4 x Ar), 134.2 (Ar), 133.8 (Ar), 133.0 (Ar), 132.8 (Ar), 132.1 (Ar), 129.8 (Ar), 129.6 (Ar), 127.8 (2 x Ar), 127.7 (Ar), 127.5 (Ar), 127.3 (2 x Ar), 127.1 (Ar), 126.9 (Ar), 125.8 (Ar), 125.1 (Ar), 70.0 (C-1), 64.8 (C-3), 41.6 (C-4), 38.6 (C-2), 27.0 ($C(CH_3)_3$), 19.4 ($C(CH_3)_3$). HRMS (ESI) calcd for (M+Na) $C_{30}H_{32}O_2SiNa$: 475.2069, found: 475.2064.



2.29

1-*tert*-Butyldiphenylsiloxy-1,2,3,4-tetrahydroanthra-3-one (2.29). Alcohol **2.28** (0.410 g, 0.90 mmol) was dissolved in EtOAc (15 mL), and IBX (0.709 g, 2.53 mmol) was

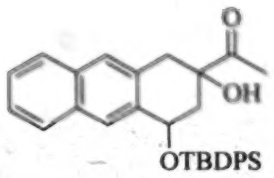
added. The white suspension was stirred for 3 h at 85 °C, whereupon the solution changed from colorless to yellow. The mixture was filtered, concentrated, and the crude product was purified by chromatography (10:1, hexanes-EtOAc) to yield **2.29** (0.380 g, 86%) as a white solid: R_f 0.70 (5:1, hexanes-EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 7.16-7.80 (m, 16 H, Ar), 5.19 (app t, 1 H, $J_{1,2ax} = J_{1,2eq} = 4.0$ Hz, H-1), 4.17 (d, 1 H, $J_{4ax,4eq} = 19.4$ Hz, H-4ax), 3.72 (d, 1 H, $J_{4ax,4eq} = 19.4$ Hz, H-4eq), 2.85 (dd, 1 H, $J_{2ax,2eq} = 17.3$ Hz, $J_{1,2ax} = 4.0$ Hz, H-2ax), 2.54 (dd, 1 H, $J_{2ax,2eq} = 17.3$ Hz, $J_{1,2eq} = 4.0$ Hz, H-2eq), 1.00 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 208.1 (C=O), 136.0 (Ar), 135.8 (2 x Ar), 133.4 (Ar), 133.2 (Ar), 133.1 (Ar), 132.1 (Ar), 131.0 (Ar), 130.0 (Ar), 129.8 (Ar), 128.1 (Ar), 128.0 (2 x Ar), 127.9 (Ar), 127.6 (2 x Ar), 127.2 (Ar), 127.0 (Ar), 126.4 (Ar), 125.9 (Ar), 125.8 (Ar), 125.7 (Ar), 70.8 (C-1), 47.4 (C-4), 44.9 (C-2), 27.0 ($C(CH_3)_3$), 19.3 ($C(CH_3)_3$). HRMS (ESI) calcd for (M+Na) $C_{30}H_{30}O_2SiNa$: 473.1913, found: 473.1907.



2.30

1-*tert*-Butyldiphenylsiloxy-3-hydroxyl-3-isopropenyl-1,2,3,4-tetrahydro-anthracene (2.30). Cerium chloride heptahydrate (2.31 g, 9.35 mmol) and a magnetic stir bar were placed in a flask and heated to 140–142 °C in vacuo (0.1 Torr) for 24 h. The flask was

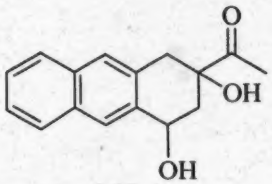
allowed cooled to rt, and ketone **2.29** (1.20 g, 2.67 mmol) and THF (10 mL) were added. The reaction mixture was vigourously stirred for 1.5 h at which point the mixture had become a yellow paste. Isopropenylmagnesium bromide 0.5 M in THF (9.6 mL, 4.81 mmol) was added over 5 min at 0 °C and the solution was stirred for 5 h. The mixture was then treated with a satd aq soln of NH_4Cl (30 mL), and EtOAc (30 mL) was added. The mixture was filtered through Celite and the aq layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried over Na_2SO_4 and purified by chromatography (15:1, hexanes-EtOAc) to yield **2.30** (0.99 g, 75%) as a clear oil: R_f 0.68 (5:1, hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.16-7.82 (m, 16 H, Ar), 5.14 (app t, 1 H, $J_{1,2ax} = J_{1,2eq} = 4.5$ Hz, H-1), 5.07 (s, 1 H, alkene), 4.85 (s, 1 H, alkene), 4.18 (s, 1 H, 3°-OH), 3.27 (d, 1 H, $J_{4ax,4eq} = 16.3$ Hz, H-4ax), 3.18 (d, 1 H, $J_{4ax,4eq} = 16.3$ Hz, H-4eq), 2.30 (dd, 1 H, $J_{2ax,2eq} = 14.1$ Hz, $J_{1,2ax} = 4.5$ Hz, H-2ax), 2.12 (dd, 1 H, $J_{2ax,2eq} = 14.1$ Hz, $J_{1,2eq} = 4.5$ Hz, H-2eq), 1.78 (s, 3 H, CH_3), 1.03 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 149.9 (Alkene), 136.2 (3 x Ar), 136.0 (Ar), 135.2 (Ar), 134.8 (Ar), 133.3 (Ar), 133.0 (Ar), 132.0 (Ar), 130.1 (Ar), 130.0 (Ar), 129.7 (Ar), 127.9 (Ar), 127.8 (Ar), 127.7 (2 x Ar), 127.6 (2 x Ar), 127.4 (Ar), 126.9 (Ar), 125.9 (Ar), 125.1 (Ar), 109.9 (Alkene), 73.5 (C-3), 71.0 (C-1), 42.1 (C-4), 41.4 (C-2), 27.0 (=CCH_3), 19.3 ($C(CH_3)_3$), 18.7 ($C(CH_3)_3$). HRMS (ESI) calcd for (M+Na) $C_{33}H_{36}O_2SiNa$: 515.2382, found: 515.2377.



2.31

1-*tert*-butyldiphenylsiloxy-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (2.31).

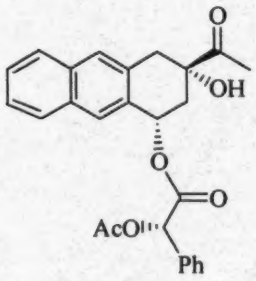
To a solution of alkene **2.30** in dioxane-water (4:1, 10 mL) was added 2,6-lutidine (0.574 g, 5.36 mmol), OsO_4 (2.5% in 2-methyl-2-propanol, 0.600 mL, 0.053 mmol) and $NaIO_4$ (1.15 g, 5.36 mmol). The reaction mixture was stirred for 12 h, and water (20 mL) and then CH_2Cl_2 (20 mL) were added. The organic layer was separated and the aq layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated and purified by column chromatography (10:1, hexanes-EtOAc) to afford **2.31** (0.35 g, 53%) as a white solid: R_f 0.63 (5:1, hexanes-EtOAc); IR υ_{max} cm^{-1}: 1712 (s); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 7.26-7.84 (m, 16 H, Ar), 5.16 (app t, 1 H, $J_{1,2ax} = J_{1,2eq} = 4.5$ Hz, H-1), 4.97 (s, 1 H, 3°-OH), 3.25-3.35 (m, 2 H, H-4ax, H-4eq), 2.10-2.25 (m, 5 H, $=CCH_3$, H-2ax, H-2eq), 1.03 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 212.0 (C=O), 136.1 (4 x Ar), 136.1 (Ar), 135.0 (Ar), 133.3 (Ar), 133.1 (Ar), 132.7 (Ar), 132.0 (Ar), 131.3 (Ar), 130.2 (Ar), 129.9 (Ar), 128.0 (2 x Ar), 127.9 (Ar), 127.7 (Ar), 127.6 (Ar), 127.5 (Ar), 127.1 (Ar), 126.1 (Ar), 125.4 (Ar), 78.5 (C-3), 70.4 (C-1), 39.2 (C-4, C-2), 27.0 ($C(O)CH_3$), 24.4 ($C(CH_3)$), 19.3 ($C(CH_3)$). HRMS (ESI) calcd for (M+Na) $C_{32}H_{34}O_3SiNa$: 517.2175, found: 517.2169.



2.32

1-Hydroxy-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (2.32). Ketone **2.31** (0.34 g, 0.688 mmol) was dissolved in THF (5 mL) and tetrabutylammonium fluoride in 1.0 M THF (0.215 g, 0.825 mmol) was added to the solution. The reaction mixture was stirred for 20 min, concentrated and purified by chromatography (2:1, hexanes-EtOAc) to yield **2.32** (0.130 g, 75%) as an oil: R_f 0.35 (1:1, hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.98 (s, 1 H, Ar), 7.83-7.87 (m, 1 H, Ar), 7.75-7.79 (m, 1 H, Ar), 7.63 (s, 1 H, Ar), 7.43-7.48 (m, 2 H, Ar), 5.12-5.17 (m, 1 H, H-1), 4.47 (s, 1 H, 3°-OH), 3.63 (d, 1 H, $J_{2°\text{-OH},1}$ = 8.9 Hz, 2°-OH), 3.40 (d, 1 H, $J_{4ax,4eq}$ = 16.4 Hz, H-4ax), 3.08 (dd, 1 H, $J_{4ax,4eq}$ = 16.4 Hz, $J_{2eq,4eq}$ = 2.3 Hz, H-4eq), 2.46 (dd, 1 H, $J_{2ax,2eq}$ = 14.1 Hz, $J_{1,2ax}$ = 4.6 Hz, H-2ax), 2.40 (s, 3 H, C(O)CH_3), 2.32 (ddd, 1 H, $J_{2ax,2eq}$ = 14.1 Hz, $J_{1,2eq}$ = 4.6 Hz, $J_{2eq,4eq}$ = 2.3 Hz, H-2eq); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 210.9 (C=O), 135.5 (Ar), 133.4 (Ar), 132.6 (Ar), 129.7 (Ar), 129.2 (Ar), 127.9 (Ar), 127.8 (Ar), 127.1 (Ar), 126.4 (Ar), 125.7 (Ar), 78.7 (C-3), 67.6 (C-1), 38.6 (C-4), 37.4 (C-2), 24.0 (C(O)CH_3). HRMS (ESI) calcd for (M+Na) $C_{16}H_{16}O_3Na$: 279.0997, found: 279.0992.

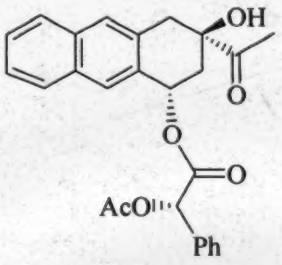
3.3.1. Procedure for the Resolution of 1,2,3,4-Tetrahydro-anthranyl Core



2.33

(1*S*,3*S*)-1-Hydroxy-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydroanthracenyl (2*S*)-2-(acetyloxy)-2-phenylethanoate (2.33). Compound **2.32** (0.212 g, 0.827 mmol), (*S*)-(+)-*O*-acetylmandelic acid (0.161 g, 0.827 mmol), and *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC·HCl, 1.58 g, 8.27 mmol), were dissolved in CH_2Cl_2 (10 mL). 4-(dimethylamino) pyridine (DMAP, 0.018 g, 0.149 mmol) was added, and the reaction mixture was stirred at room temperature for 24 h. The mixture was concentrated and purified by chromatography (60:1, CH_2Cl_2-acetone) to yield **2.33** (0.224 g, 63%) as an oil: R_f 0.49 (20:1, CH_2Cl_2-$(CH_3)_2O$); $[\alpha]_D$ +32.8 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.74 (d, 1 H, J = 8.1, Ar), 7.58-7.65 (m, 2 H, Ar), 7.32-7.49 (m, 8 H, Ar), 6.22 (app t, 1 H, $J_{1,2ax} = J_{1,2eq}$ = 4.9 Hz, H-1), 5.88 (s, 1 H, C*H*(OAc)), 3.60 (s, 1 H, 3°-OH), 3.20 (d, 1 H, $J_{4ax,4eq}$ = 16.0 Hz, H-4ax), 3.05 (d, 1 H, $J_{4ax,4eq}$ = 16.0 Hz, H-4eq), 2.40 (dd, 1 H, $J_{2ax,2eq}$ = 15.2 Hz, $J_{1,2ax}$ = 4.9 Hz, H-2ax), 2.27-2.36 (m, 4 H, H-2eq, C(O)CH_3), 2.20 (s, 3 H, OC(O)CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 202.7 (C=O),

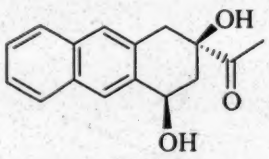
170.8 (C=O, mandalate), 168.4 (C=O, acetyl), 133.6 (Ar), 133.1 (Ar), 132.2 (Ar), 131.3 (Ar), 130.6 (Ar), 129.4 (Ar), 128.9 (Ar), 128.8 (Ar), 128.0 (Ar), 127.9 (Ar), 127.7 (2 x Ar), 127.6 (Ar), 127.1 (Ar), 126.6 (Ar), 125.8 (Ar), 75.1 (*C*H(OAc)), 71.0 (C-1), 38.5 (C-4), 37.1 (C-2), 24.4 ($C(O)CH_3$), 20.7 ($OC(O)CH_3$). HRMS (ESI) calcd for (M+Na) $C_{26}H_{24}O_6Na$: 455.1471, found: 455.1466.



2.34

(1*R*,3*R*)-1-Hydroxy-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracenyl (2*S*)-2-(acetyloxy)-2-phenylethanoate (2.34). Product **2.34** (0.104 g, 29%) was obtained as a clear oil: R_f 0.68 (20:1, CH_2Cl_2-acetone); $[\alpha]_D$ –32.8 (*c* 0.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.76-7.84 (m, 3 H, Ar), 7.63 (s, 1 H, Ar), 7.34-7.50 (m, 7 H, Ar), 6.36 (app t, 1 H, $J_{1,2ax} = J_{1,2eq} = 4.2$ Hz, H-1), 5.95 (s, 1 H, C*H*(OAc)), 3.23 (d, 1 H, $J_{4ax,4eq} = 16.0$ Hz, H-4ax), 3.00-3.10 (m, 2 H, H-4eq, 3°-OH), 2.40 (dd, 1 H, $J_{2ax,2eq} = 15.2$ Hz, $J_{1,2ax} = 4.2$ Hz, H-2ax), 2.22 (m, 6 H, $OC(O)CH_3$, $C(O)CH_3$), 1.98 (ddd, 1 H, $J_{2ax,2eq} = 15.2$ Hz, $J_{1,2eq} = 4.2$ Hz, $J_{2eq,4eq} = 1.8$ Hz, H-2eq); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 202.6 (C=O), 170.6 (C=O, mandalate), 168.0 (C=O, acetyl), 133.7 (Ar), 133.4 (Ar), 132.4 (Ar),

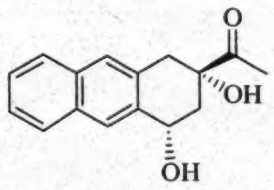
131.1 (Ar), 130.4 (Ar), 129.5 (Ar), 128.9 (Ar), 128.6 (2 x Ar), 128.1 (Ar), 127.9 (Ar), 127.6 (2 x Ar), 127.1 (Ar), 126.8 (Ar), 125.9 (Ar), 74.8 (*C*H(OAc)), 70.5 (C-1), 38.6 (C-4), 37.0 (C-2), 24.3 ($C(O)CH_3$), 20.7 ($OC(O)CH_3$). HRMS (ESI) calcd for (M+Na) $C_{26}H_{24}O_6Na$: 455.1471, found: 455.1465.



2.35

(1*R*,3*R*)-1-Hydroxy-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (2.35). Compound **2.34** (0.197 g, 0.456 mmol) was dissolved in dry CH_3OH (10 mL) and K_2CO_3 (0.095 g, 0.684 mmol) was added. The mixture was stirred for 24 h, concentrated, diluted with CH_2Cl_2 (10 mL), and washed with water (10 mL). The organic layer was dried over Na_2SO_4 and concentrated to yield **2.35** (0.111 g, 95%) as a clear oil. R_f 0.35 (1:1, hexanes-EtOAc); $[\alpha]_D$ -12.0 (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.98 (s, 1 H, Ar), 7.83-7.87 (m, 1 H, Ar), 7.75-7.79 (m, 1 H, Ar), 7.63 (s, 1 H, Ar), 7.43-7.48 (m, 2 H, Ar), 5.12-5.17 (m, 1 H, H-1), 4.47 (s, 1 H, 3°-OH), 3.63 (d, 1 H, $J_{2°\text{-}OH,1}$ = 8.9 Hz, 2°-OH), 3.40 (d, 1 H, $J_{4ax,4eq}$ = 16.4 Hz, H-4ax), 3.08 (dd, 1 H, $J_{4ax,4eq}$ = 16.4 Hz, $J_{2eq,4eq}$ = 2.3 Hz, H-4eq), 2.46 (dd, 1 H, $J_{2ax,2eq}$ = 14.1 Hz, $J_{1,2ax}$ = 4.6 Hz, H-2ax), 2.40 (s, 3 H, $C(O)CH_3$), 2.32 (ddd, 1 H, $J_{2ax,2eq}$ = 14.1 Hz, $J_{1,2eq}$ = 4.6 Hz, $J_{2eq,4eq}$ = 2.3 Hz, H-2eq); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 210.9 (C=O), 135.5 (Ar), 133.4 (Ar), 132.6 (Ar), 129.7 (Ar), 129.2 (Ar),

127.9 (Ar), 127.8 (Ar), 127.1 (Ar), 126.4 (Ar), 125.7 (Ar), 78.7 (C-3), 67.6 (C-1), 38.6 (C-4), 37.4 (C-2), 24.0 ($C(O)CH_3$). HRMS (ESI) calcd for (M+Na) $C_{16}H_{16}O_3Na$: 279.0997, found: 279.0992.

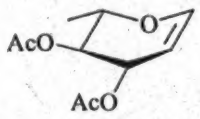


2.12

(1*S*,3*S*)-1-Hydroxy-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (2.12). Compound **2.33** (0.300 g, 0.694 mmol) was dissolved in dry CH_3OH (10 mL) and K_2CO_3 (0.143 g, 1.04 mmol) was added. The mixture was stirred for 24 h, concentrated, diluted with CH_2Cl_2 (10 mL), and washed with water (10 mL). The organic layer was dried over Na_2SO_4 and concentrated to yield **2.12** (0.169 g, 95%) as a clear oil. R_f 0.35 (1:1, hexanes-EtOAc); $[\alpha]_D$ +18.2 (*c* 0.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.98 (s, 1 H, Ar), 7.83-7.87 (m, 1 H, Ar), 7.75-7.79 (m, 1 H, Ar), 7.63 (s, 1 H, Ar), 7.43-7.48 (m, 2 H, Ar), 5.12-5.17 (m, 1 H, H-1), 4.47 (s, 1 H, 3°-OH), 3.63 (d, 1 H, $J_{2°\text{-}OH,1}$ = 8.9 Hz, 2°-OH), 3.40 (d, 1 H, $J_{4ax,4eq}$ = 16.4 Hz, H-4ax), 3.08 (dd, 1 H, $J_{4ax,4eq}$ = 16.4 Hz, $J_{2,4ax}$ = 2.3 Hz, H-4eq), 2.46 (dd, 1 H, $J_{2ax,2eq}$ = 14.1 Hz, $J_{1,2ax}$ = 4.6 Hz, H-2ax), 2.40 (s, 3 H, CH_3), 2.32 (ddd, 1 H, $J_{2ax,2eq}$ = 14.1 Hz, $J_{1,2eq}$ = 4.6 Hz, $J_{2eq,4eq}$ = 2.3 Hz, H-2eq); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 210.9 (C=O), 135.5 (Ar), 133.4 (Ar), 132.6 (Ar), 129.7 (Ar), 129.2 (Ar), 127.9 (Ar), 127.8 (Ar), 127.1 (Ar), 126.4 (Ar), 125.7 (Ar), 78.7 (C-3), 67.6 (C-1), 38.6

(C-4), 37.4 (C-2), 24.0 ($C(O)CH_3$). HRMS (ESI) calcd for (M+Na) $C_{16}H_{16}O_3Na$: 279.0997, found: 279.0994.

3.4. Procedure for the Preparation of Monosaccharide Donors



2.41

3,4-Di-*O*-acetyl-1,5-anhydro-2,6-dideoxy-L-*arabino*-hex-1-enitol (2.41).[1]

Ac_2O (100 mL) containing 4 drops of perchloric acid was cooled to 0 °C, and L-rhamnose (20 g, 0.109 mol) was added in small portions. The reaction mixture was stirred for 4 h at rt. The mixture was cooled to 0 °C and CH_3OH (40 mL) was added slowly and stirring was continued for an additional 30 min. The solution was concentrated, and the residue was dissolved in CH_2Cl_2 (75 mL). The solution was washed with a satd aq soln of $NaHCO_3$, and the organic layer was dried over Na_2SO_4, filtered and concentrated to give 1,2,3,4-tetra-*O*-acetyl-L-rhamnopyranose. The crude product was used without any further purification. Thus, the product was dissolved in a mixture of AcOH (10 mL);Ac_2O (10 mL) and 45% HBr in AcOH (48 mL). The reaction mixture was stirred for 18 h, and the crude product was subsequently added to the following prepared stock solution.

In a three-necked round bottom flask equipped with a mechanical stirrer, NaOAc (100 g,

1.2 mol) in 50% aq acetic acid (240 mL) were added. The solution was cooled to -10 °C, and zinc dust (72 g, 1.1 mol) and cupric sulphate pentahydrate (7.2 g, 28.8 mmol) dissolved in water (25 mL) were added. The solution was stirred vigorously with frequent venting of gas. At a rate such that the temperature was kept below 5 °C, the crude mixture of glycosyl bromide prepared above was added dropwise over 2 h. The reaction mixture was further stirred for 4 h, and then filtered and the solids were washed with a cold 50% aq soln of AcOH (80 mL). The filtrate was extracted with cold CH_2Cl_2 (3 x 150 mL) and the combined organic layers were washed with a cold satd aq soln of $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography (8:1, hexanes-EtOAc) to yield **2.41** (17.5 g, 76%) as a colorless oil: R_f 0.68 (2:1, hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 6.39 (dd, 1 H, $J_{1,2}$ = 6.7 Hz, $J_{1,3}$ = 1.5 Hz, H-1), 5.31 (dddd, 1 H, $J_{3,4}$ = 6.0 Hz, $J_{2,3}$ = 3.0 Hz, $J_{1,3}$ = 1.5 Hz, $J_{3,5}$ = 0.7 Hz, H-3), 4.97-5.02 (m, 1 H, H-4), 4.75 (dd, 1 H, $J_{1,2}$ = 6.7 Hz, $J_{2,3}$ = 3.0 Hz, H-2), 4.04-4.11 (m, 1 H, H-5), 2.04 (s, 3 H, $OC(O)CH_3$), 2.00 (s, 3 H, $OC(O)CH_3$), 1.28 (d, 3 H, $J_{5,6}$ = 6.6 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.6 (C=O), 169.8 (C=O), 145.9 (C-1), 98.7 (C-2), 72.5 (C-5), 71.8 (C-4), 68.3 (C-3), 21.0 ($OC(O)CH_3$), 20.8 ($OC(O)CH_3$), 16.5 (C-6). HRMS (ESI) calcd for (M+Na) $C_{10}H_{14}O_5Na$: 237.0739, found: 237.0732.

2.44

Methyl 4-*O*-acetyl-2,3,6-trideoxy-α,β-L-*erythro*-hex-2-enopyranoside (2.44).[1]

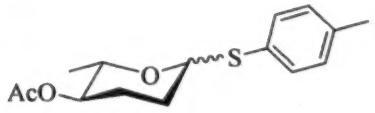
3,4-Di-*O*-acetyl-1,5-anhydro-2,6-dideoxy-L-*arabino*-hex-1-enitol **2.41** (5.04 g, 23.5 mmol) was dissolved in CH_2Cl_2 (40 mL) and CH_3OH (2.82 mL, 70.2 mmol). To this solution was added dropwise $SnCl_4$ (0.275 mL, 2.35 mmol) and the reaction mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of a satd aq soln of $NaHCO_3$, the layers were separated, and the organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated. The crude product was purified by chromatography (8:1, hexanes-EtOAc) to yield **2.44** α:β 5:2, (3.63 g, 83%) as a colorless oil: R_f 0.66 (6:1, hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 5.84-5.89 (m, 0.29 H, H-2β) 5.82-5.84 (m, 0.29 H, H-3β), 5.80 (br d, $J_{2,3}$ = 10.5 Hz, 0.71 H, H-3α), 5.75 (ddd, 0.71 H, $J_{2,3}$ = 10.5 Hz, $J_{1,2}$ = 2.6 Hz, $J_{2,4}$ = 2.0 Hz, H-2α), 5.00-5.06 (m, 0.58 H, H-1β, H-4β), 5.06-5.10 (m, 0.71 H, H-4α), 4.81 (br s, 0.71 H, H-1α), 3.89 (dq, 0.71 H, $J_{4,5}$ = 9.2 Hz, $J_{5,6}$ = 6.3 Hz, H-5α), 3.81 (q, 0.29 H, $J_{5,6}$ = 6.3 Hz, H-5β), 3.41 (s, 0.87 H, OC(O)CH_3, β), 3.39 (s, 2.13 H, OC(O)CH_3, α), 1.27 (d, 2.13 H, $J_{5,6}$ = 6.3 Hz, H-6α), 1.19 (d, 0.87 H, $J_{5,6}$ = 6.3 Hz, H-6β); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.4 (C=O, α), 170.3 (C=O, β), 130.2 (C-2, β), 129.7 (C-3, α), 127.8 (C-3, β), 127.6 (C-2, α), 96.7 (C-1, β), 95.4 (C-1, α), 71.2 (C-5, β), 70.8 (C-4, α), 69.5 (C-4, β), 64.7 (C-5, α), 55.7 (OCH_3, α), 54.8 (OCH_3, β), 21.1 (OC(O)CH_3, α), 21.0 (OC(O)CH_3, β), 18.4 (C-6, β), 17.9 (C-6, α). HRMS (ESI) calcd for (M+Na) $C_9H_{14}O_4Na$: 209.0790, found: 209.0785.

2.45

Methyl 4-*O*-acetyl-2,3,6-trideoxy-α,β-L-*erythro*-hexopyranoside (2.45).

Methyl 4-*O*-acetyl-2,3,6-deoxy-α,β-L-*erythro*-hex-2-enopyranoside **2.44** (3.40 g, 18.0 mmol) was dissolved in EtOAc (100 mL) and 10% Pd/C (0.102 g) was added. The reaction mixture was stirred under H_2 at room temperature and normal pressure for 3 h. Once the starting material was fully consumed as determined by TLC, the mixture was filtered through Celite and concentrated. The crude product was purified by chromatography (8:1, hexanes-EtOAc) to yield **2.45** α:β 6:1 (3.31 g, 97%) as a colorless oil: R_f 0.62 (6:1, hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 4.60 (d, 0.85 H, $J_{1,2ax}$ = 1.4 Hz, H-1α), 4.39-4.44 (m, 0.85 H, H-4 α), 4.45-4.50 (m, 0.15 H, H-4 β), 4.36 (dd, 0.15 H, $J_{1,2ax}$ = 9.1 Hz, $J_{1,2eq}$ = 2.2 Hz, H-1β), 3.74 (dq, 0.85 H, $J_{4,5}$ = 9.6 Hz, $J_{5,6}$ = 6.3 Hz, H-5α), 3.48 (dq, 0.15 H, $J_{4,5}$ = 9.0 Hz, $J_{5,6}$ = 6.2 Hz, H-5β), 3.44 (s, 0.45 H, OCH_3, β), 3.32 (s, 2.55 H, OCH_3, α), 2.08-2.15 (m, 0.15 H, H-3ax β), 2.05 (s, 0.45 H, $OC(O)CH_3$, β), 2.03 (s, 2.55 H, $OC(O)CH_3$, α), 1.83-1.87 (m, 0.15 H, H-2eq β), 1.87-1.92 (m, 0.85 H, H-3ax α), 1.70-1.82 (m, 2.55 H, H-2ax α, H-2eq α, H-3eq α), 1.58 (dddd, 0.15 H, $J_{2ax,2eq}$ = 13.3 Hz, $J_{2ax,3ax}$ = 13.2 Hz, $J_{1,2ax}$ = 9.1 Hz, $J_{2ax,3eq}$ = 4.1 Hz, H-2ax β), 1.40-1.49 (m, 0.15 H, H-3eq β), 1.20 (d, 0.45 H, $J_{5,6}$ = 6.2 Hz, H-6β), 1.12 (d, 2.55 H, $J_{5,6}$ = 6.3 Hz, H-6α); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.2 (C=O, α), 170.1 (C=O, β), 102.3 (C-1, β), 97.3 (C-1, α), 73.4 (C-4, α), 73.1 (C-5, β), 72.9 (C-4, β), 66.3 (C-5, α), 56.2

(OCH_3, β), 54.4 (OCH_3, α), 29.9 (C-2, β), 29.0 (C-2, α), 27.1 (C-3, β), 24.0 (C-3, α), 21.1 (OC(O)CH_3, α), 21.0 (OC(O)CH_3, β), 18.0 (C-6, β), 17.8 (C-6, α). HRMS (ESI) calcd for (M+Na) $C_9H_{16}O_4Na$: 211.0946, found: 211.0940.

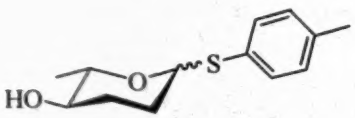


2.46

***p*-Tolyl 4-*O*-acetyl-2,3,6-trideoxy-1-thio-α,β-L-*erythro*-hexopyranoside (2.46).**

Methyl 4-*O*-acetyl-2,3,6-deoxy-α,β-L-*erythro*-hexopyranoside **2.45** (3.03 g, 16.0 mmol) was dissolved in CH_2Cl_2 (30 mL). To this solution was added *p*-thiocresol (3.97 g, 32.0 mmol) and $Sc(OTf)_3$ (0.030 g), and the mixture was stirred for 10 h. The mixture was diluted with water (100 mL), and the aq layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, and concentrated. The crude product was purified by chromatography (20:1, hexanes-EtOAc) to yield **2.46** α:β 6:1, (3.41 g, 76%) as a colorless oil: R_f 0.55 (6:1, hexanes-EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 7.34-7.42 (m, 2 H, Ar, α+β), 7.08-7.13 (m, 2 H, Ar, α+β), 5.44 (br d, 0.85 H, $J_{1,2ax}$ = 4.7 Hz, H-1α), 4.70 (dd, 0.15 H, $J_{1,2ax}$ = 11.5 Hz, $J_{1,2eq}$ = 2.2 Hz, H-1β), 4.53 (ddd, 0.85 H, $J_{3ax,4}$ = 14.0 Hz, $J_{4,5}$ = 9.4 Hz, $J_{3eq,4}$ = 4.6 Hz, H-4α), 4.47 (ddd, 0.15 H, $J_{3ax,4}$ = 14.2 Hz, $J_{4,5}$ = 9.5 Hz, $J_{3eq,4}$ = 4.9 Hz, H-4β), 4.32 (dq, 0.85 H, $J_{4,5}$ = 9.4 Hz, $J_{5,6}$ = 6.2 Hz, H-5α), 3.48 (dq, 0.15 H, $J_{4,5}$ = 9.5 Hz, $J_{5,6}$ = 6.2 Hz, H-5β), 2.35 (s, 0.45 H, Ar-CH_3, β),

2.32 (s, 2.55 H, Ar-CH_3, α), 2.19-2.24 (m, 0.85 H, H-2ax α), 2.13-2.18 (m, 0.15 H, H-3ax β), 2.08 (s, 0.45 H, OC(O)CH_3, β), 2.05-2.11 (m, 0.3 H, H-2ax β, H-2eq β), 2.04 (s, 2.55 H, OC(O)CH_3, α), 1.99-2.05 (m, 0.85 H, H-2eq α), 1.75-1.80 (m, 0.85 H, H-3ax α), 1.81-1.87 (m, 0.15 H, H-3eq β), 1.48-1.59 (m, 0.85 H, H-3eq α), 1.24 (d, 0.45 H, $J_{5,6}$ = 6.2 Hz, H-6β), 1.17 (d, 2.55 H, $J_{5,6}$ = 6.2 Hz, H-6α); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 170.3 (C=O, α), 170.2 (C=O, β), 137.5 (Ar, β), 137.1 (Ar, α), 132.2 (2 x Ar, β), 131.8 (2 x Ar, α), 131.3 (Ar, α), 130.2 (Ar, β), 129.7 (2 x Ar, α), 129.6 (2 x Ar, β), 84.6 (C-1, β), 84.5 (C-1, α), 76.5 (C-5, β), 73.5 (C-4, α), 72.7 (C-4, β), 67.4 (C-5, α), 31.0 (C-2, β), 30.1 (C-2, α), 29.8 (C-3, α), 25.6 (C-3, β), 21.2 (OC(O)CH_3, β), 21.1 (OC(O)CH_3, α), 21.0 (Ar-CH_3, α+β), 18.3 (C-6, β), 17.7 (C-6, α). HRMS (ESI) calcd for (M+Na) $C_{15}H_{20}O_3NaS$: 303.1031, found: 303.1027. Anal. Calcd. for: C, 64.26; H, 7.19; S, 11.44. Found: C, 64.27; H, 7.35; S, 11.40.

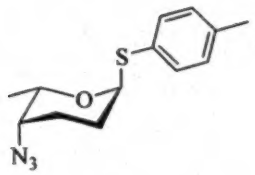


2.47

***p*-Tolyl 2,3,6-trideoxy-1-thio-α,β-L-*erythro*-hexopyranoside (2.47).**

p-Tolyl 4-*O*-acetyl-2,3,6-deoxy-1-thio-α,β-L-*erythro*-hexopyranoside **2.46** (2.62 g, 9.3 mmol) was dissolved in dry CH_3OH (100 mL), and a solution of $NaOCH_3$ (1 mL, 2 M) was added. The mixture was stirred for 3 h and was neutralized with IR-120 Amberlite®

(H^+). Filtration, followed by removal of solvent, afforded a residue that was purified by chromatography (7:1, hexanes-EtOAc) to yield **2.47** α:β 6:1, (2.26 g, 98%) as a colorless oil: R_f 0.32 (5:1, hexanes-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$, δ_H) 7.34-7.42 (m, 2 H, Ar, α+β), 7.08-7.13 (m, 2 H, Ar, α+β), 5.43 (br d, 0.85 H, $J_{1,2ax}$ = 4.3 Hz, H-1α), 4.70 (dd, 0.15 H, $J_{1,2ax}$ = 11.5 Hz, $J_{1,2eq}$ = 2.2 Hz, H-1β), 4.1 (dq, 0.85 H, $J_{4,5}$ = 9.1 Hz, $J_{5,6}$ = 6.3 Hz, H-5α), 3.23-3.37 (m, 1.15 H, H-4α, H-4β, H-5β), 2.35 (s, 0.45 H, Ar-CH_3, β), 2.32 (s, 2.55 H, Ar-CH_3, α), 1.94-2.24 (m, 2.15 H, H-2ax α, H-2eq α, H-2ax β, H-2eq β, H-3eq β), 1.69-1.86 (m, 1 H, H-3ax α, H-3ax β), 1.54 (br s, 1 H, OH), 1.44-1.58 (m, 0.85 H, H-3eq α), 1.34 (d, 0.45 H, $J_{5,6}$ = 5.8 Hz, H-6β), 1.27 (d, 2.55 H, $J_{5,6}$ = 6.3 Hz, H-6α); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 137.3 (Ar, β), 137.0 (Ar, α), 131.9 (2 x Ar, β), 131.8 (2 x Ar, α), 131.5 (Ar, α), 130.7 (Ar, β), 129.7 (2 x Ar, α), 129.5 (2 x Ar, β), 84.6 (C-1α, C-1β), 79.0 (C-5, β), 72.3 (C-4, α), 71.4 (C-4, β), 70.2 (C-5, α), 33.3 (C-2, β), 31.5 (C-2, α), 30.7 (C-3, α), 29.1 (C-3, β), 21.1 (Ar-CH_3, α+β), 18.2 (C-6, β), 17.7 (C-6, α). HRMS (ESI) calcd for (M+Na) $C_{13}H_{18}O_2NaS$: 261.0925, found: 261.0920.

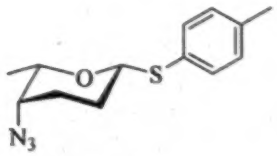


2.36α

***p*-Tolyl 4-azido-2,3,4,6-tetradeoxy-1-thio-α-L-*threo*-hexopyranoside (2.36α).**

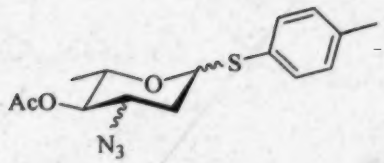
p-Tolyl 2,3,6-deoxy-1-thio-α,β-L-*erythro*-hexopyranoside **2.47** (2.08 g, 8.7 mmol) was dissolved in CH_2Cl_2 (30 mL) and Et_3N (3.64 mL, 26.1 mmol) was added. MsCl (1.01 mL, 13.1 mmol) was added dropwise at 0 °C to the mixture, and the solution was stirred at room temperature for 3 h, at which point all the alcohol was consumed (TLC). The reaction mixture was washed with water (80 mL), and the aq layer was extracted with CH_2Cl_2. The combined organic phases were washed with water, dried over Na_2SO_4, and concentrated to give an orange residue. This residue was dissolved in DMF (30 mL) and NaN_3, (2.83 g, 43.5 mmol) was added, and the mixture was heated to 110 °C for 24 h. After completion of the reaction, the mixture was diluted with CH_2Cl_2 (50 mL), and the organic layer was washed with water (30 mL), brine, dried over Na_2SO_4, and concentrated. The crude product was purified by chromatography (10:1, hexanes-EtOAc) to yield **2.36α** (1.27 g, 55%) and **2.36β** (0.21 g, 9%) α:β 6:1, both as colorless oils. **(2.36α)**: R_f 0.90 (5:1, hexanes-EtOAc); $[\alpha]_D$ -186.7 (*c* 1.3, $CHCl_3$); IR υ_{max} cm^{-1}: 2097 (s); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.08-7.38 (m, 4 H, Ar), 5.54 (br d, 1 H, $J_{1,2ax}$ = 5.4 Hz, H-1), 4.51 (dq, 1 H, $J_{5,6}$ = 6.5 Hz, $J_{4,5}$ = 1.5 Hz, H-5), 3.50-3.57 (m, 1 H, H-4), 2.31-2.39 (m, 1 H, H-2eq), 2.33 (s, 3 H, Ar-CH_3), 2.15 (dddd, 1 H, $J_{2ax,3ax}$ = 14.1 Hz, $J_{3ax,3eq}$ =

14.1 Hz, $J_{2eq,3ax}$ = 4.2 Hz, $J_{3ax,4}$ = 3.3 Hz, H-3ax), 2.00-2.07 (m, 1 H, H-2ax), 1.79-1.85 (m, 1 H, H-3eq), 1.23 (d, 3 H, $J_{5,6}$ = 6.5 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 137.1 (Ar), 131.6 (2 x Ar), 131.2 (Ar), 129.7 (2 x Ar), 84.9 (C-1), 66.2 (C-5), 60.0 (C-4), 25.2 (C-2), 24.5 (C-3), 21.1 (Ar-CH_3), 17.8 (C-6). HRMS (ESI) calcd for $C_{13}H_{17}N_3ONaS$: 286.0990, found: 286.0987.



2.36β

***p*-Tolyl 4-azido-2,3,4,6-tetradeoxy-1-thio-β-L-*threo*-hexopyranoside (2.36β).** R_f 0.70 (5:1, hexanes-EtOAc); $[\alpha]_D$ +171.0 (*c* 0.9, $CHCl_3$); IR υ_{max} cm^{-1}: 2098 (s); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.08-7.38 (m, 4 H, Ar), 4.73 (dd, 1 H, $J_{1,2ax}$ = 11.1 Hz, $J_{1,2eq}$ = 2.5 Hz, H-1), 3.66 (dq, 1 H, $J_{5,6}$ = 6.3 Hz, $J_{4,5}$ = 1.7 Hz, H-5), 3.40 (br m, 1 H, H-4), 2.33 (s, 3 H, Ar-CH_3), 2.16-2.22 (m, 1 H, H-3ax), 1.78-1.97 (m, 3 H, H-2ax, H-2eq, H-3eq), 1.31 (d, 3 H, $J_{5,6}$ = 6.3 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 137.4 (Ar), 132.2 (2 x Ar), 130.4 (Ar), 129.5 (2 x Ar), 85.3 (C-1), 75.7 (C-5), 58.8 (C-4), 28.9 (C-2), 25.9 (C-3), 21.1 (Ar-CH_3), 18.4 (C-6). HRMS (ESI) calcd for $C_{13}H_{17}N_3ONaS$: 286.0990, found: 286.0985.

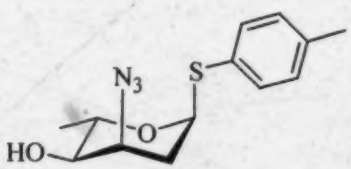


2.48

***p*-Tolyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-1-thio-L-*arabino*/*ribo*-hexopyranoside (2.48).** A suspension of 3,4-di-*O*-acetyl-1,5-anhydro-2,6-dideoxy-L-*arabino*-hex-1-enitol **2.41** (3.02 g, 14.1 mmol) in water (20 mL) was stirred for 2 h at 80 °C. After cooling to 25 °C, to the resulting solution were added, HOAc (3 mL) and sodium azide (1.62 g, 20.0 mmol) and the reaction mixture was stirred for 24 h. The crude material was washed with a satd aq soln of $NaHCO_3$, and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, and concentrated to yield a colorless oil. The crude mixture (2.87 g, 95%), was used without further purification or characterization.

This mixture (2.87 g, 11.2 mmol) was dissolved in CH_2Cl_2 (25 mL) and pyridine (7.5 mL) and acetic anhydride (7.5 mL) were added. The reaction mixture was stirred for 24 h, and the mixture was diluted with ice-water (100 mL). The aq layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were washed with 1 M HCl, a satd aq soln of $NaHCO_3$, water, brine, dried over Na_2SO_4, and concentrated (3.10 g, 88%) to give a yellow oil. The crude product was used without further purification. This crude mixture (3.10 g, 12.1 mmol) was dissolved in CH_2Cl_2 (30 mL). To this solution was added thiocresol (3.12 g, 25.0 mmol) and $Sc(OTf)_3$ (0.016 g), and the mixture was stirred for 10 h. The mixture was diluted with water (100 mL), and the aq layer was extracted with

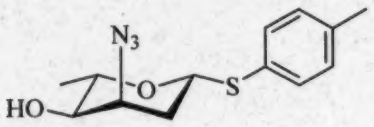
CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, and concentrated to yield crude **2.48** (2.99 g, 77%) as a clear oil. Purification and separation of the different anomers were not possible and therefore the product was deprotected before separation was attempted.



2.49

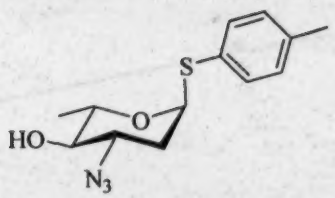
***p*-Tolyl 3-azido-2,3,6-trideoxy-1-thio-α-L-*ribo*-hexopyranoside (2.49).** Crude **2.48** (2.99 g, 9.30 mmol) was dissolved in dry CH_3OH (60 mL), and a solution of $NaOCH_3$ (0.5 mL, 2M) was added. The mixture was stirred for 24 h and was neutralized with IR-120 Amberlite® (H^+). Filtration followed by removal of solvent afforded **2.49-2.52** as a mixture, which could be purified by chromatography (20:1, hexanes-EtOAc) to yield **2.49** (0.164 g, 8%), **2.50** (0.539 g, 26%), **2.51** (0.624 g, 30%), and **2.52** (0.370 g, 18%). **(2.49)**: R_f 0.28 (10:1, hexanes-EtOAc); IR υ_{max} cm^{-1}: 2097 (s); ^1H NMR (300 MHz, $CDCl_3$, δ_H) 7.33-7.38 (m, 2 H, Ar), 7.10-7.16 (m, 2 H, Ar), 5.35 (d, 1 H, $J_{1,2ax}$ = 4.1 Hz, H-1), 4.27 (dq, 1 H, $J_{4,5}$ = 8.7 Hz, $J_{5,6}$ = 6.3 Hz, H-5), 4.08 (q, 1 H, $J_{3,4} = J_{2ax,3} = J_{2eq,3}$ = 3.4 Hz, H-3), 3.40 (dd, 1 H, $J_{4,5}$ = 8.7 Hz, $J_{3,4}$ = 3.4 Hz, H-4), 2.38-2.45 (m, 2 H, H-2ax, H-2eq), 2.34 (s, 3 H, Ar-CH_3), 1.30 (d, 3 H, $J_{5,6}$ = 6.3 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 137.3 (Ar), 132.7 (Ar), 131.5 (2 x Ar), 129.7 (2 x Ar), 82.5 (C-1), 72.3 (C-4),

66.1 (C-5) 59.6 (C-3), 34.6 (C-2), 21.1 (Ar-CH_3), 17.3 (C-6). HRMS (ESI) calcd for $C_{13}H_{17}N_3O_2NaS$: 302.0939, found: 302.0932.



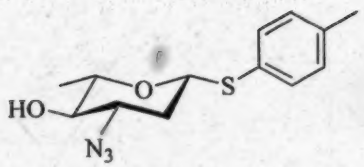
2.50

***p*-Toly1 3-azido-2,3,6-trideoxy-1-thio-β-L-*ribo*-hexopyranoside (2.50).** R_f 0.29 (10:1, hexanes-EtOAc); IR υ_{max} cm^{-1}: 2097 (s); ^1H NMR (300 MHz, $CDCl_3$, δ_H) 7.33-7.38 (m, 2 H, Ar), 7.10-7.16 (m, 2 H, Ar), 4.96 (dd, 1 H, $J_{1,2ax}$ = 11.7 Hz, $J_{1,2eq}$ = 2.6 Hz, H-1), 4.09 (ddd, 1 H, $J_{3,4}$ = $J_{2ax,3}$ = $J_{2eq,3}$ = 3.3 Hz, H-3), 3.63 (dq, 1 H, $J_{4,5}$ = 9.3 Hz, $J_{5,6}$ = 6.2 Hz, H-5), 3.37 (dd, 1 H, $J_{4,5}$ = 9.3 Hz, $J_{3,4}$ = 3.3 Hz, H-4), 2.34 (s, 3 H, Ar-CH_3), 2.26 (ddd, 1 H, $J_{2ax,2eq}$ = 14.4 Hz, $J_{1,2eq}$ = 2.6 Hz, $J_{2eq,3}$ = 3.3 Hz, H-2eq), 1.99 (ddd, 1 H, $J_{2ax,2eq}$ = 14.4 Hz, $J_{1,2ax}$ = 11.7 Hz, $J_{2ax,3}$ = 3.3 Hz, H-2ax), 1.32 (d, 3 H, $J_{5,6}$ = 6.2 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 137.8 (Ar), 132.4 (2 x Ar), 129.7 (2 x Ar), 129.6 (Ar), 79.7 (C-1), 73.3 (C-4), 72.4 (C-5) 61.8 (C-3), 36.1 (C-2), 21.1 (Ar-CH_3), 18.0 (C-6). HRMS (ESI) calcd for $C_{13}H_{17}N_3O_2NaS$: 302.0939, found: 302.0935.



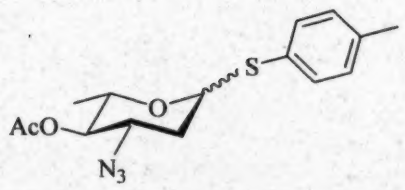
2.51

***p*-Tolyl 3-azido-2,3,6-trideoxy-1-thio-α-L-*arabino*-hexopyranoside (2.51).** R_f 0.36 (10:1, hexanes-EtOAc); $[\alpha]_D$ -175.8 (*c* 1.1, $CHCl_3$); IR υ_{max} cm^{-1}: 2105 (s); ^1H NMR (300 MHz, $CDCl_3$, δ_H) 7.33-7.38 (m, 2 H, Ar), 7.10-7.16 (m, 2 H, Ar), 5.5 (d, 1 H, $J_{1,2ax}$ = 5.6 Hz, H-1), 4.23 (dq, 1 H, $J_{4,5}$ = 9.3 Hz, $J_{5,6}$ = 6.2 Hz, H-5), 3.78 (ddd, 1 H, $J_{2ax,3}$ = 12.5 Hz, $J_{3,4}$ = 9.4 Hz, $J_{2eq,3}$ = 4.9 Hz, H-3), 3.18 (ddd, 1 H, $J_{4,5}$ = 9.3 Hz, $J_{3,4}$ = 9.4 Hz, $J_{2eq,4}$ = 3.6 Hz, H-4), 2.27-2.42 (m, 1 H, H-2eq), 2.34 (s, 3 H, Ar-CH_3), 2.11 (ddd, 1 H, $J_{2ax,2eq}$ = 13.5 Hz, $J_{2ax,3}$ = 12.5 Hz, $J_{1,2ax}$ = 5.6 Hz, H-2ax), 1.30 (d, 3 H, $J_{5,6}$ = 6.2 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 137.7 (Ar), 132.1 (2 x Ar), 130.5 (Ar), 129.8 (2 x Ar), 83.7 (C-1), 76.7 (C-4), 68.5 (C-5) 61.1 (C-3), 35.8 (C-2), 21.1 (Ar-CH_3), 17.5 (C-6). HRMS (ESI) calcd for $C_{13}H_{17}N_3O_2NaS$: 302.0939, found: 302.0933. Anal. Calcd. for: C, 55.89; H, 6.13; N, 15.04; S 11.48. Found: C, 56.17; H, 6.09; N, 14.82; S, 11.10.



2.52

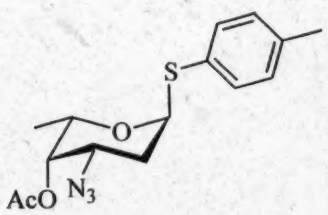
***p*-Tolyl 3-azido-2,3,6-trideoxy-1-thio-β-L-*arabino*-hexopyranoside (2.52).** R_f 0.30 (10:1, hexanes-EtOAc); $[\alpha]_D$ +71.4 (*c* 0.8, $CHCl_3$); IR υ_{max} cm^{-1}: 2110 (s); ^1H NMR (300 MHz, $CDCl_3$, δ_H) 7.33-7.38 (m, 2 H, Ar), 7.10-7.16 (m, 2 H, Ar), 4.73 (dd, 1 H, $J_{1,2ax}$ = 11.7 Hz, $J_{1,2eq}$ = 2.0 Hz, H-1), 3.46 (ddd, 1 H, $J_{2ax,3}$ = 11.9 Hz, $J_{3,4}$ = 9.6 Hz, $J_{2eq,3}$ = 5.0 Hz, H-3), 3.35 (dq, 1 H, $J_{4,5}$ = 9.1 Hz, $J_{5,6}$ = 6.1 Hz, H-5), 3.17 (dd, 1 H, $J_{4,5}$ = 9.1 Hz, $J_{3,4}$ = 9.6 Hz, H-4), 2.31-2.39 (m, 1 H, H-2eq), 2.34 (s, 3 H, Ar-CH_3), 1.78 (ddd, 1 H, $J_{2ax,2eq}$ = 12.9 Hz, $J_{2ax,3}$ = 11.9 Hz, $J_{1,2ax}$ = 11.7 Hz, H-2ax), 1.38 (d, 3 H, $J_{5,6}$ = 6.1 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 138.1 (Ar), 132.6 (2 x Ar), 129.7 (Ar), 129.4 (2 x Ar), 82.3 (C-1), 76.4 (C-4), 75.2 (C-5) 64.0 (C-3), 36.3 (C-2), 21.1 (Ar-CH_3), 18.0 (C-6). HRMS (ESI) calcd for $C_{13}H_{17}N_3O_2NaS$: 302.0939, found: 302.0936. Anal. Calcd. for: C, 55.89; H, 6.13; N, 15.04; S, 11.48. Found: C, 55.89; H, 5.99; N, 14.89; S, 11.33.



2.37

***p*-Tolyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-1-thio-α,β-L-*arabino*-hexopyranoside (2.37).** Compounds **2.51** and **2.52** (1.25 g, 4.47 mmol) were dissolved in CH_2Cl_2 (20 mL) and pyridine (5.0 mL) and then Ac_2O (5.0 mL) were added. The reaction mixture was stirred for 4 h, and the mixture was diluted with ice water (50 mL). The aq layer was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic layers were washed with 1 M HCl, a satd aq soln of $NaHCO_3$, water, brine, dried over Na_2SO_4, concentrated and purified by column chromatography (20:1, hexanes-EtOAc) to yield **2.37** α:β 1:1, (1.22 g, 85%) as a yellow solid: R_f 0.22 (20:1, hexanes-EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 7.34-7.42 (m, 3 H, Ar, α+β), 7.08-7.13 (m, 3 H, Ar, α+β), 5.51 (br d, 0.5 H, $J_{1,2ax}$ = 5.2 Hz, H-1α), 4.68-4.74 (m, 1 H, H-1β, H-4α), 4.64 (dd, 0.5 H, $J_{4,5} = J_{3,4}$ = 9.4 Hz, H-4β), 4.32 (dq, 0.5 H, $J_{4,5}$ = 9.7 Hz, $J_{5,6}$ = 6.2 Hz, H-5α), 3.88 (ddd, 0.5 H, $J_{2ax,3}$ = 14.6 Hz, $J_{3,4}$ = 9.8 Hz, $J_{2eq,3}$ = 4.9 Hz, H-3α), 3.56 (ddd, 0.5 H, $J_{2ax,3}$ = 14.8 Hz, $J_{3,4}$ = 9.7 Hz, $J_{2eq,3}$ = 5.1 Hz, H-3β), 3.45 (dq, 0.5 H, $J_{4,5}$ = 9.4 Hz, $J_{5,6}$ = 6.2 Hz, H-5β), 2.30-2.40 (m, 0.5 H, H-2eq α), 2.36 (s, 1.5 H, $OC(O)CH_3$, β), 2.34 (s, 1.5 H, $OC(O)CH_3$, α), 2.08-2.17 (m, .05 H, H-2ax α), 2.16 (s, 1.5 H, Ar-CH_3, α), 2.12 (s, 1.5 H, Ar-CH_3, β), 1.72-1.85 (m, 1 H, H-2ax β, H-2eq β), 1.23 (d, 1.5 H, $J_{5,6}$ = 6.2 Hz, H-6β), 1.17 (d, 1.5 H, $J_{5,6}$ = 6.2 Hz, H-6α); ^{13}C

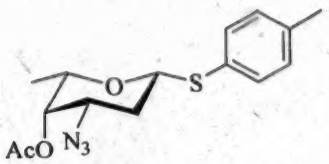
NMR (100 MHz, $CDCl_3$, δ_C) 170.0 (C=O, α), 169.9 (C=O, β), 138.3 (Ar, β), 137.8 (Ar, α), 133.1 (2 x Ar, α+β), 132.1 (2 x Ar, α+β), 130.2 (Ar, α), 129.8 (2 x Ar, α+β), 129.7 (2 x Ar, α+β), 128.7 (Ar, β), 83.5 (C-1, α), 82.1 (C-1, β), 75.7 (C-4, α), 74.8 (C-4, β), 74.7 (C-5, β), 66.8 (C-5, α), 61.3 (C-3, β), 58.4 (C-3, α), 36.5 (C-2, β), 35.9 (C-2, α), 21.1 (Ar-CH_3, α+β), 20.8 (OC(O)CH_3, α+β), 17.8 (C-6, β), 17.3 (C-6, α). HRMS (ESI) calcd for (M+Na) $C_{15}H_{19}N_3O_3NaS$: 344.1045, found: 344.1040.



2.38α

***p*-Tolyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-1-thio-α-L-*lyxo*-hexopyranoside (2.38α).** *p*-Tolyl 3-azido-2,3,6-deoxy-1-thio-α,β-L-*arabino*-hexopyranoside **2.51** and **2.52** (0.10 g, 0.358 mmol) were dissolved in CH_2Cl_2 (5.0 mL) and pyridine (2.0 mL) was added. A solution of triflic anhydride (0.100 mL, 0.394 mmol) was added and the mixture was cooled to -15 °C and stirred for 4.5 h. The reaction mixture was poured into water (10 mL), and the organic layer was separated. The aq layer was extracted with CH_2Cl_2 (2 x 10 mL), and the combined organic layers were washed with a satd aq soln of $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated to give a yellow oil. The oil was dried in vacuo for 30 min, and then dissolved in CH_3CN (5 mL). Tetrabutylammonium acetate

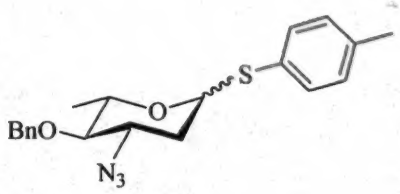
(0.216 g, 0.716 mmol) was added and the reaction mixture was stirred for 70 min. The crude product was added to water (25 mL), the organic layer was separated, and the aq layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated and purified by column chromatography (20:1, hexanes-EtOAc) to yield **2.38α** (0.057 g, 49%) and **2.38β** (0.028 g, 25%) α:β 1:1, both as yellow solids over two steps. **(2.38α)**: R_f 0.70 (5:1, hexanes-EtOAc); $[\alpha]_D$ -231.9 (*c* 1.2, $CHCl_3$); IR υ_{max} cm^{-1}: 2103 (s), 1747 (s), 1223 (s); ^1H NMR (300 MHz, $CDCl_3$, δ_H) 7.33-7.38 (m, 2 H, Ar), 7.10-7.16 (m, 2 H, Ar), 5.50 (d, 1 H, $J_{1,2ax}$ = 5.7 Hz, H-1), 5.20-5.23 (m, 1 H, H-4), 4.46-4.54 (m, 1 H, H-5), 3.18 (ddd, 1 H, $J_{2ax,3}$ = 13.0 Hz, $J_{3,4}$ = 4.7 Hz, $J_{2eq,3}$ = 3.0 Hz, H-3), 2.45 (ddd, 1 H, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 13.0 Hz, $J_{1,2ax}$ = 5.7 Hz, H-2ax), 2.34 (s, 3 H, $OC(O)CH_3$) 2.19 (s, 3 H, Ar-CH_3), 2.10-2.18 (m, 1 H, H-2eq), 1.14 (d, 3 H, $J_{5,6}$ = 6.5 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 170.4 (C=O), 137.6 (Ar), 131.9 (2 x Ar), 129.8 (2 x Ar), 128.3 (Ar), 83.9 (C-1), 70.1 (C-4), 66.0 (C-5) 55.5 (C-3), 30.2 (C-2), 21.1 (Ar-CH_3), 20.7 ($OC(O)CH_3$), 17.5 (C-6). HRMS (ESI) calcd for (M+Na) $C_{15}H_{19}N_3O_3NaS$: 344.1045, found: 344.1042.



2.38β

***p*-Tolyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-1-thio-β-L-*lyxo*-hexopyranoside (2.38β).**

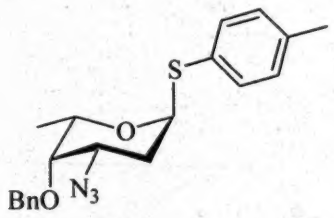
R_f 0.64 (5:1, hexanes-EtOAc); $[\alpha]_D$ +48.9 (*c* 0.9, $CHCl_3$); IR υ_{max} cm^{-1}: 2100 (s), 1745 (s), 1229 (s); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 7.41-7.44 (m, 2 H, Ar), 7.12-7.16 (m, 2 H, Ar), 5.12 (br s, 1 H, H-4), 4.73 (dd, 1 H, $J_{1,2ax}$ = 11.2 Hz, $J_{1,2eq}$ = 2.5 Hz, H-1), 3.63 (dq, 1 H, $J_{5,6}$ = 6.5 Hz, $J_{4,5}$ = 1.1 Hz, H-5), 3.51 (ddd, 1 H, $J_{2ax,3}$ = 12.0 Hz, $J_{3,4}$ = 5.2 Hz, $J_{2eq,3}$ = 3.1 Hz, H-3), 2.35 (s, 3 H, $OC(O)CH_3$), 2.19 (s, 3 H, Ar-CH_3), 2.01-2.18 (m, 2 H, H-2ax, H-2eq), 1.22 (d, 3 H, $J_{5,6}$ = 6.5 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 170.5 (C=O), 134.0 (Ar), 132.4 (2 x Ar), 129.7 (2 x Ar), 129.6 (Ar), 83.0 (C-1), 73.9 (C-4), 69.0 (C-5) 58.7 (C-3), 31.0 (C-2), 21.1 (Ar-CH_3), 20.7 ($OC(O)CH_3$), 17.1 (C-6). HRMS (ESI) calcd for (M+Na) $C_{15}H_{19}N_3O_3NaS$: 344.1045, found: 344.1040.



2.39

***p*-Tolyl 3-azido-4-*O*-benzyl-2,3,6-trideoxy-1-thio-α,β-L-*arabino*-hexopyranoside (2.39).** Compound **2.37** (0.100 g, 0.311 mmol) was dissolved in dry CH_3OH (8 mL) and K_2CO_3 (0.043 g, 0.31 mmol) was added. The mixture was stirred for 24 h, concentrated, diluted with CH_2Cl_2 (10 mL), and washed with water (10 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude product was dissolved in dry DMF (10 mL) and cooled to 0 °C. NaH (0.015g, 0.622 mmol) and benzyl bromide (0.106 g, 0.622 mmol) were added, and the reaction mixture was stirred for 3 h. The mixture was diluted with water (5 mL), extracted with EtOAc (2 x 10 mL), dried over Na_2SO_4, concentrated, and purified by column chromatography (25:1, hexanes-EtOAc) to yield **2.39** α:β 1:1, (0.070 g, 61%) as a clear oil. R_f 0.62 (5:1, hexanes-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$, δ_H) 7.06-7.42 (m, 9 H, Ar α+β), 5.48 (d, 0.5 H, $J_{1,2ax}$ = 5.2 Hz, H-1α), 4.82-4.96 (m, 1 H, PhCH_2 α), 4.60-4.74 (m, 1.5 H, H-1β, PhCH_2 β), 4.30 (dq, 0.5 H, $J_{4,5}$ = 9.4 Hz, $J_{5,6}$ = 6.2 Hz, H-5α), 3.92 (ddd, 0.5 H, $J_{2ax,3}$ = 14.1 Hz, $J_{3,4}$ = 9.3 Hz, $J_{2eq,3}$ = 4.8 Hz, H-3α), 3.59 (dq, 0.5 H, $J_{2ax,3}$ = 14.1 Hz, $J_{3,4}$ = 9.2 Hz, $J_{2eq,3}$ = 4.7 Hz, H-3β), 3.58 (dq, 0.5 H, $J_{4,5}$ = 9.2 Hz, $J_{5,6}$ = 6.2 Hz, H-5β), 3.00-3.06 (m, 0.5 H, H-4α), 3.06-3.12 (m, 0.5 H, H-4β), 2.39-2.42 (m, 3 H, Ar-CH_3, α+β), 2.32-2.34 (m, 0.5 H, H-2ax α), 2.35-2.38 (m, 0.5 H, H-2ax β), 2.02-2.14 (m, 0.5 H, H-2eq α), 1.69-1.83 (m, 0.5 H, H-2eq β), 1.38 (d, 1.5 H,

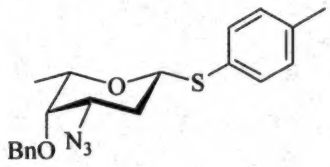
$J_{5,6}$ = 6.2 Hz, H-6β) 1.31 (d, 1.5 H, $J_{5,6}$ = 6.2 Hz, H-6α); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C), 137.9 (Ar), 137.5 (Ar), 137.4 (Ar), 132.5 (2 x Ar), 132.0 (3 x Ar), 130.5 (Ar), 129.7 (2 x Ar), 129.6 (2 x Ar), 129.4 (Ar), 128.4 (2 x Ar), 128.2 (2 x Ar), 128.1 (4 x Ar), 128.0 (Ar), 127.9 (Ar), 84.1 (C-1α), 83.5 (C-1β), 82.9 (C-4α), 82.2 (C-4β), 76.6 (C-5β), 75.2 ((PhCH_2), 75.1 ((PhCH_2), 68.1 (C-5α), 63.6 (C-3β), 60.6 (C-3α), 37.0 (C-2β), 36.3 (C-2α), 21.1 (Ar-CH_3 α), 21.0 (Ar-CH_3 β), 18.3 (C-6β), 17.8 (C-6α). HRMS (ESI) calcd for (M+Na) $C_{20}H_{23}N_3O_2NaS$: 392.1409, found: 392.1402.



2.40α

***p*-Tolyl 3-azido-4-*O*-benzyl-2,3,6-deoxy-1-thio-α-L-*lyxo*-hexopyranoside (2.40α).** A mixture of compounds **2.38α** and **2.38β** (0.100 g, 0.311 mmol) were dissolved in dry CH_3OH (8 mL) and K_2CO_3 (0.043 g, 0.31 mmol) was added. The mixture was stirred for 24 h, concentrated, diluted with CH_2Cl_2 (10 mL), and washed with water (10 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude product was dissolved in dry DMF (10 mL) and cooled to 0 °C. NaH (0.015g, 0.622 mmol) and benzyl bromide (0.106 g, 0.622 mmol) were added, and the reaction mixture was stirred for 3 h. The mixture was diluted with water (5 mL), extracted with EtOAc (2 x 10 mL),

dried over Na_2SO_4, concentrated, and purified by column chromatography (25:1, hexanes-EtOAc) to yield **2.40α** (0.056 g, 49%), and **2.40β** (0.022 g, 19%) α:β 1:1, both as clear oils. **(2.40α)**: R_f 0.85 (5:1, hexanes-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$, δ_H) 7.27-7.46 (m, 7 H, Ar), 7.06-7.16 (m, 2 H, Ar), 5.65 (d, 1 H, $J_{1,2ax}$ = 5.6 Hz, H-1), 4.90 (d, 1 H, J = 11.2 Hz, PhCH_2), 4.63 (d, 1 H, J = 11.2 Hz, PhCH_2), 4.33 (q, 1 H, $J_{5,6}$ = 6.4 Hz, H-5), 3.73 (ddd, 1 H, $J_{2ax,3}$ = 12.9 Hz, $J_{3,4}$ = 4.3 Hz, $J_{2eq,3}$ = 2.8 Hz, H-3), 3.55-3.59 (m, 1 H, H-4), 2.60 (ddd, 1 H, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 12.9 Hz, $J_{1,2ax}$ = 5.6 Hz, H-2ax), 2.34 (s, 3 H, Ar-CH_3), 2.05-2.14 (m, 1 H, H-2eq), 1.19 (d, 3 H, $J_{5,6}$ = 6.4 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C), 137.7 (Ar), 137.2 (Ar), 131.5 (2 x Ar), 130.8 (Ar), 129.6 (2 x Ar), 128.3 (2 x Ar), 128.2 (2 x Ar), 127.8 (Ar), 83.8 (C-1), 76.6 (C-4), 75.3 (PhCH_2), 67.4 (C-5), 57.1 (C-3), 29.9 (C-2), 21.0 (Ar-CH_3), 16.9 (C-6). HRMS (ESI) calcd for (M+Na) $C_{20}H_{23}N_3O_2NaS$: 392.1409, found: 392.1403.



2.40β

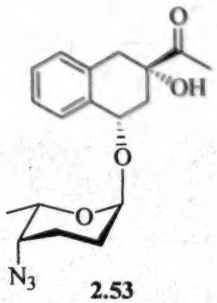
***p*-Tolyl 3-azido-4-*O*-benzyl-2,3,6-deoxy-1-thio-β-L-*lyxo*-hexopyranoside (2.40β).** R_f 0.67 (5:1, hexanes-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$, δ_H) 7.27-7.46 (m, 7 H, Ar), 7.04-7.13 (m, 2 H, Ar), 4.85 (d, 1 H, J = 11.3 Hz, PhCH_2), 4.60-4.72 (m, 2 H, H-1,

PhCH_2), 3.30-3.55 (m, 3 H, H-3, H-4, H-5), 2.20-2.40 (m, 4 H, H-2ax, Ar-CH_3), 2.05-2.15 (m, 1 H, H-2eq), 1.25 (d, 3 H, $J_{5,6}$ = 6.4 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C), 137.8 (Ar), 137.5 (Ar), 132.2 (2 x Ar), 129.9 (Ar), 129.4 (2 x Ar), 128.1 (2 x Ar), 128.0 (2 x Ar), 127.6 (Ar), 82.8 (C-1), 75.9 (C-4), 75.3 (C-5), 75.1 (PhCH_2), 60.3 (C-3), 30.5 (C-2), 21.0 (Ar-CH_3), 17.4 (C-6). HRMS (ESI) calcd for (M+Na) $C_{20}H_{23}N_3O_2NaS$: 392.1409, found: 392.1404.

3.5. Preparation of 1,2,3,4-Tetrahydro-naphthyl and 1,2,3,4-Tetrahydro -anthranyl Glycosides.

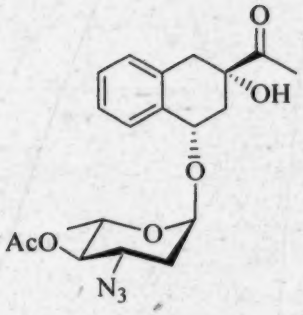
3.5.1. General Procedure for the Glycosylation of 1,2,3,4-Tetrahydro-naphthyl and 1,2,3,4-Tetrahydro-anthranyl cores.

A mixture of thioglycoside (0.5 mmol) and compound **2.11** or **2.12** (0.5 mmol) and DTBMP (1.46 mmol) were dissolved in CH_2Cl_2 (10 mL). Molecular sieves (4 Å, freshly activated) was added and the reaction mixture was stirred for 1.5 h under an inert atmosphere. The reaction mixture was cooled to 0 °C and powdered $AgPF_6$ (1.46 mmol) was added, and stirring was maintained for 2-3 h. Et_3N (5 mL) was added, followed by filtration through Celite, concentration and purification by column chromatography afforded the desired products.



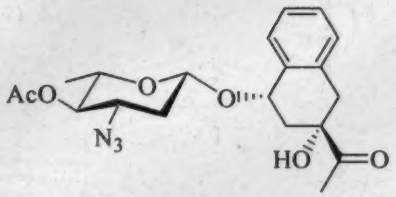
2.53

(1*S*,3*S*)-1-*O*-(4-azido-2,3,4,6-tetradeoxy-α-L-*threo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (2.53). Yield 85%. R_f 0.42 (3:1, hexanes-EtOAc); $[\alpha]_D$ -55.1 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.18-7.38 (m, 4 H, Ar), 5.50 (d, 1 H, $J_{1,2ax}$ = 3.0 Hz, H-1), 4.94 (app t, 1 H, $J_{1,2ax} = J_{1,2eq}$ = 3.4 Hz, H-1_a), 4.78 (s, 1 H, 3°-OH), 4.12 (dq, 1 H, $J_{5,6}$ = 6.5 Hz, $J_{4,5}$ = 1.7 Hz, H-5), 3.54 (br s, 1 H, H-4), 3.20 (d, 1 H, $J_{4ax,4eq}$ = 17.1 Hz, H-4_aax), 3.02 (d, 1 H, $J_{4ax,4eq}$ = 17.1 Hz, H-4_aeq), 2.36 (s, 3 H, $C(O)CH_3$), 2.22-2.31 (m, 2 H, H-2_aax, H-2_aeq), 2.07-2.16 (m, 1 H, H-3ax), 1.90-2.02 (m, 2 H, H-2eq, H-3eq), 1.42-1.49 (m, 1 H, H-2ax), 1.30 (d, 3 H, $J_{5,6}$ = 6.5 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 212.2 (C=O), 133.8 (Ar), 132.2 (Ar), 130.2 (Ar), 130.0 (Ar), 129.1 (Ar), 126.1 (Ar), 94.2 (C-1), 78.2 (C-3_a), 71.4 (C-1_a), 66.1 (C-5), 59.8 (C-4), 39.0 (C-4_a), 36.0 (C-2_a), 24.7 ($C(O)CH_3$), 23.9 (C-3), 22.9 (C-2), 18.0 (C-6). HRMS (ESI) calcd for (M+Na) $C_{18}H_{23}N_3O_4Na$: 368.1586, found: 368.1583.



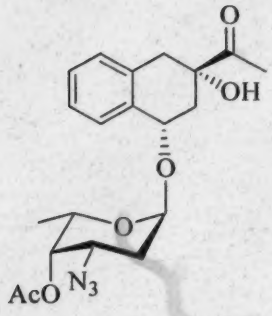
2.54

(1*S*,3*S*)-1-*O*-(4-*O*-acetyl-3-azido-2,3,6-deoxy-α-L-*arabino*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (2.54). Yield 39%. R_f 0.38 (3:1, hexanes-EtOAc); $[\alpha]_D$ -157.3 (*c* 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.19-7.36 (m, 4 H, Ar), 5.17 (d, 1 H, $J_{1,2ax}$ = 4.1 Hz, H-1), 4.93 (app t, 1 H, $J_{1,2ax} = J_{1,2eq}$ = 3.3 Hz, H-1_a), 4.72 (dd, 1 H, $J_{4,5} = J_{3,4}$ = 9.7 Hz, H-4), 4.48 (s, 1 H, 3°-OH), 3.82-3.96 (m, 2 H, H-3, H-5), 3.18 (d, 1 H, $J_{4ax,4eq}$ = 16.9 Hz, H-4_aax), 3.06 (d, 1 H, $J_{4ax,4eq}$ = 16.9 Hz, H-4_aeq), 2.35 (s, 3 H, $C(O)CH_3$), 2.27-2.31 (m, 2 H, H-2_aax, H-2_aeq), 2.16 (s, 3 H, $OC(O)CH_3$), 2.07 (ddd, 1 H, $J_{2ax,2eq} = J_{2ax,3}$ = 13.1 Hz, $J_{1,2ax}$ = 4.1 Hz, H-2ax), 1.81 (dd, 1 H, $J_{2ax,2eq}$ = 13.1 Hz, $J_{2eq,3}$ = 4.1 Hz, H-2eq), 1.25 (d, 3 H, $J_{5,6}$ = 6.3 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 211.9 (C=O), 170.0 ($OC(O)CH_3$), 133.9 (Ar), 131.8 (Ar), 130.1 (Ar), 130.0 (Ar), 129.4 (Ar), 126.3 (Ar), 93.7 (C-1), 78.0 (C-3_a), 75.4 (C-1_a), 71.8 (C-4), 66.8 (C-5), 57.4 (C-3), 39.0 (C-4_a), 36.3 (C-2_a), 35.1 (C-2), 24.7 ($C(O)CH_3$), 20.9 ($OC(O)CH_3$), 17.5 (C-6). HRMS (ESI) calcd for (M+Na) $C_{20}H_{25}N_3O_6Na$: 426.1641, found: 426.1632.



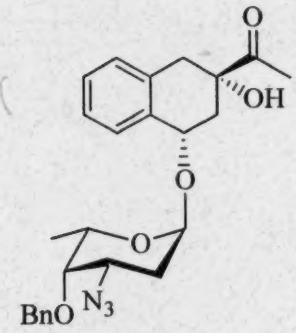
2.54β

(1*S*,3*S*)-1-*O*-(4-*O*-acetyl-3-azido-2,3,6-deoxy-β-L-*arabino*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (2.54β). Yield 31%. R_f 0.17 (3:1, hexanes-EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 7.11-7.48 (m, 4 H, Ar), 5.12 (app t, 1 H, $J_{1,2sx}$= $J_{1,2eq}$ = 2.9 Hz, H-1$_a$), 4.81 (dd, 1 H, $J_{1,2ax}$ = 9.6 Hz, $J_{1,2eq}$ = 1.9 Hz, H-1), 4.70 (dd, 1 H, $J_{4,5}$ = $J_{3,4}$ = 9.5 Hz, H-4), 4.14 (s, 1 H, 3°-OH), 3.48-3.61 (m, 2 H, H-3, H-5), 3.10 (d, 1 H, $J_{4ax,4eq}$ = 16.7 Hz, H-4$_a$ax), 2.99 (d, 1 H, $J_{4ax,4eq}$ = 16.7 Hz, H-4$_a$eq), 2.36 (s, 3 H, C(O)CH_3), 2.16-2.28 (m, 3 H, H-2ax, H-2$_a$ax, H-2$_a$eq), 2.14 (s, 3 H, OC(O)CH_3), 1.67-1.76 (m, 1 H, H-2eq), 1.29 (d, 3 H, $J_{5,6}$ = 6.1 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 212.3 (C=O), 169.9 (O*C*(O)CH_3), 133.1 (Ar), 133.0 (Ar), 130.7 (Ar), 130.0 (Ar), 128.9 (Ar), 126.9 (Ar), 96.5 (C-1), 77.8 (C-3$_a$), 74.8 (C-1$_a$), 72.5 (C-4), 71.1 (C-5), 59.8 (C-3), 39.0 (C-4$_a$), 36.3 (C-2$_a$), 34.0 (C-2), 24.7 (C(O)*C*H_3), 20.9 (OC(O)*C*H_3), 17.6 (C-6). HRMS (ESI) calcd for (M+Na) $C_{20}H_{25}N_3O_6Na$: 426.1641, found: 426.1635.



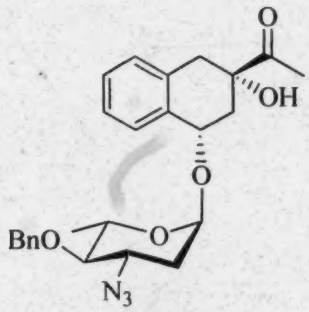
2.55

(1*S*,3*S*)-1-*O*-(4-*O*-acetyl-3-azido-2,3,6-deoxy-α-L-*lyxo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (2.55). Yield 70%. R_f 0.31 (3:1, hexanes-EtOAc); $[\alpha]_D$ -135.2 (*c* 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 7.18-7.36 (m, 4 H, Ar), 5.18-5.24 (m, 2 H, H-4, H-1), 4.93 (app t, 1 H, $J_{1,2ax} = J_{1,2eq} = 3.3$ Hz, H-1_a), 4.45 (s, 1 H, 3°-OH), 4.13 (q, 1 H, $J_{5,6} = 6.4$ Hz, H-5), 3.84 (ddd, 1 H, $J_{2ax,3} = 13.0$ Hz, $J_{3,4} = 4.7$ Hz, $J_{2eq,3} = 3.4$ Hz, H-3), 3.18 (d, 1 H, $J_{4ax,4eq} = 17.0$ Hz, H-4_aax), 3.14 (d, 1 H, $J_{4ax,4eq} = 17.0$ Hz, H-4_aeq), 2.33 (s, 3 H, $C(O)CH_3$), 2.25-2.28 (m, 2 H, H-2_aax, H-2_aeq), 2.19 (s, 3 H, $OC(O)CH_3$), 2.07 (ddd, 1 H, $J_{2ax,2eq} = J_{2ax,3} = 13.0$ Hz, $J_{1,2ax} = 4.1$ Hz, H-2ax), 1.81 (dd, 1 H, $J_{2ax,2eq} = 13.0$ Hz, $J_{2eq,3} = 3.4$ Hz, H-2eq), 1.22 (d, 3 H, $J_{5,6} = 6.4$ Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 211.9 (C=O), 170.3 ($OC(O)CH_3$), 133.8 (Ar), 131.6 (Ar), 129.9 (Ar), 129.2 (Ar), 129.1 (Ar), 126.1 (Ar), 94.2 (C-1), 77.9 (C-3_a), 71.9 (C-1_a), 69.8 (C-4), 65.8 (C-5), 54.2 (C-3), 38.9 (C-4_a), 36.1 (C-2_a), 29.3 (C-2), 24.5 ($C(O)CH_3$), 20.6 ($OC(O)CH_3$), 16.7 (C-6). HRMS (ESI) calcd for (M+Na) $C_{20}H_{25}N_3O_6Na$: 426.1641, found: 426.1638.



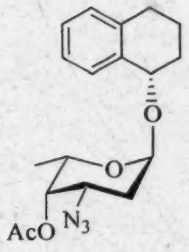
2.56

(1*S*,3*S*)-1-*O*-(3-azido-4-*O*-benzyl-2,3,6-deoxy-α-L-*lyxo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (2.56). Yield 60%. R_f 0.28 (3:1, hexanes-EtOAc); $[\alpha]_D$ -89.1 (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 7.13-7.42 (m, 9 H, Ar), 5.18 (d, 1 H, $J_{1,2ax}$ = 3.3 Hz, H-1), 4.89-4.98 (m, 2 H, H-1_a, PhCH_2), 4.62 (d, 1 H, J = 11.2 Hz , PhCH_2), 4.54 (s, 1 H, 3°-OH), 3.95 (q, 1 H, $J_{5,6}$ = 6.5 Hz, H-5), 3.70 (ddd, 1 H, $J_{2ax,3}$ = 12.8 Hz, $J_{3,4}$ = 4.5 Hz, $J_{2eq,3}$ = 2.7 Hz, H-3), 3.53 (s, 1 H, H-4), 3.17 (d, 1 H, $J_{4ax,4eq}$ = 17.1 Hz, H-4_aax), 3.02 (d, 1 H, $J_{4ax,4eq}$ = 17.1 Hz, H-4_aeq), 2.32 (s, 3 H, C(O)CH_3), 2.18-2.28 (m, 3 H, H-2_aax, H-2_aeq, H-2ax), 1.73-1.79 (m, 1 H, H-2eq), 1.22 (d, 3 H, $J_{5,6}$ = 6.5 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 212.0 (C=O), 137.5 (Ar), 133.6 (Ar), 131.8 (Ar), 130.0 (Ar), 129.9 (Ar), 129.1 (Ar), 128.5 (2 x Ar), 128.3 (2 x Ar), 127.8 (Ar), 126.1 (Ar), 94.5 (C-1), 78.0 (C-3_a), 76.6 (C-1_a), 75.3 (PhCH_2), 71.7 (C-4), 67.3 (C-5), 55.9 (C-3), 38.9 (C-4_a), 35.9 (C-2_a), 28.9 (C-2), 24.6 (C(O)CH_3), 17.1 (C-6). HRMS (ESI) calcd for (M+Na) $C_{25}H_{29}N_3O_5Na$: 474.2005, found: 474.1999.



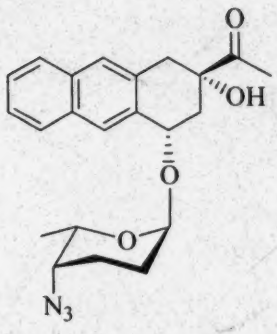
2.57

(1*S*,3*S*)-1-*O*-(3-azido-4-*O*-benzyl-2,3,6-deoxy-α-L-*arabino*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (2.57). Yield 46%. R_f 0.32 (3:1, hexanes-EtOAc); $[\alpha]_D$ -82.2 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.18-7.44 (m, 9 H, Ar), 5.02 (d, 1 H, $J_{1,2ax}$ = 4.1 Hz, H-1), 4.88-4.94 (m, 2 H, H-1_a, PhCH_2), 4.67 (d, 1 H, *J* = 10.5 Hz, PhCH_2), 4.55 (s, 1 H, 3°-OH), 3.82-3.92 (m, 2 H, H-3, H-5), 3.20 (d, 1 H, $J_{4ax,4eq}$ = 16.1 Hz, H-4_aax), 3.00-3.10 (m, 2 H, H-4, H-4_aeq), 2.35 (s, 3 H, C(O)CH_3), 2.23-2.26 (m, 2 H, H-2_aax, H-2_aeq), 2.00 (ddd, 1 H, $J_{2ax,2eq} = J_{2ax,3}$ = 13.3 Hz, $J_{1,2ax}$ = 4.1 Hz, H-2ax), 1.81 (dd, 1 H, $J_{2ax,2eq}$ = 13.3 Hz, $J_{2eq,3}$ = 4.1 Hz, H-2eq), 1.25 (d, 3 H, *J* = 6.2 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 212.3 (C=O), 137.4 (Ar), 134.1 (Ar), 131.7 (Ar), 130.1 (Ar), 130.0 (Ar), 129.3 (Ar), 128.6 (2 x Ar), 128.4 (2 x Ar), 128.1 (Ar), 126.1 (Ar), 93.3 (C-1), 83.8 (C-4), 78.1 (C-3_a), 75.4 (PhCH_2), 71.2 (C-1_a), 68.2 (C-5), 59.8 (C-3), 39.0 (C-4_a), 36.2 (C-2_a), 35.5 (C-2), 24.8 (C(O)CH_3), 18.2 (C-6). HRMS (ESI) calcd for (M+Na) $C_{25}H_{29}N_3O_5Na$: 474.2005, found: 474.2001



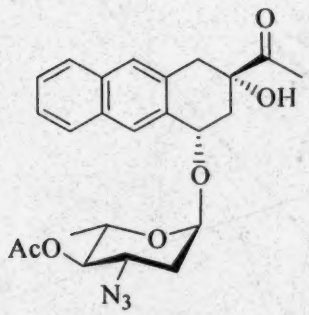
2.65

(1*S*)-1-*O*-(4-*O*-acetyl-3-azido-2,3,6-deoxy-α-L-*lyxo*-hexopyranosyl)-1,2,3,4-tetrahydro-naphthalene (2.65). Yield 50%. R_f 0.45 (6:1, hexanes-EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 7.15-7.35 (m, 4 H, Ar), 5.24 (d, 1 H, $J_{1,2ax}$ = 3.0 Hz, H-1), 5.16-5.20 (m, 1 H, H-4), 4.66 (app t, 1 H, $J_{1,2ax} = J_{1,2eq}$ = 4.5 Hz, H-1$_a$), 4.10-4.18 (m, 1 H, H-5), 3.84-3.94 (m, 1 H, H-3), 2.68-2.91 (m, 2 H, H-4$_a$ax, H-4$_a$eq), 2.20 (s, 3 H, OC(O)CH_3), 1.74-2.14 (m, 6 H, H-2ax, H-2eq, H-2$_a$ax, H-2$_a$eq, H-3$_a$ax, H-3$_a$eq), 1.38 (d, 3 H, $J_{5,6}$ = 6.6 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 170.6 (O*C*(O)CH_3), 137.6 (Ar), 135.5 (Ar), 129.3 (Ar), 127.9 (Ar), 127.8 (Ar), 125.6 (Ar), 96.4 (C-1), 74.1 (C-1$_a$), 70.3 (C-4), 65.5 (C-5), 54.7 (C-3), 29.9 (C-4$_a$), 29.2 (C-2$_a$ + C-3$_a$), 28.8 (C-2), 20.9 (OC(O)*C*H_3), 16.8 (C-6). HRMS (ESI) calcd for (M+Na) $C_{18}H_{23}N_3O_4Na$: 368.1586, found: 368.1580.



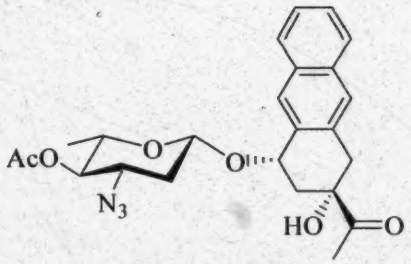
2.67

(1*S*,3*S*)-1-*O*-(4-azido-2,3,4,6-tetradeoxy-α-L-*threo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (2.67). Yield 50%. R_f 0.24 (5:1, hexanes-EtOAc); $[\alpha]_D$ -28.9 (*c* 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 7.74-7.86 (m, 3 H, Ar), 7.66 (s, 1 H, Ar), 7.43-7.51 (m, 2 H, Ar), 5.15 (d, 1 H, $J_{1,2ax}$ = 3.5 Hz, H-1_a), 5.00-5.05 (m, 1H, H-1), 4.72 (s, 1 H, 3°-OH), 4.15 (dq, 1 H, $J_{5,6}$ = 6.5 Hz, $J_{4,5}$ = 1.7 Hz, H-5), 3.56 (br s, 1 H, H-4), 3.32 (d, 1 H, $J_{4ax,4eq}$ = 16.0 Hz, H-4_aax), 3.25 (d, 1 H, $J_{4ax,4eq}$ = 16.0 Hz, H-4_aeq), 2.28-2.41 (m, 5 H, H-2_aax, H-2_aeq, C(O)CH_3), 2.22-2.31 (m, 2 H, H-3_aax, H-3_aeq), 2.12-2.22 (m, 1 H, H-3eq), 1.90-2.00 (m, 2 H, H-2ax, H-3ax), 1.40-1.47 (m, 1 H, H-2eq), 1.35 (d, 3 H, $J_{5,6}$ = 6.5 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 211.9 (C=O), 133.7 (Ar), 131.8 (Ar), 131.6 (Ar), 130.8 (Ar), 128.8 (Ar), 128.2 (Ar), 127.9 (Ar), 127.1 (Ar), 126.6 (Ar), 125.9 (Ar), 93.3 (C-1), 78.3 (C-3_a), 71.4 (C-1_a), 66.1 (C-5), 59.9 (C-4), 39.4 (C-4_a), 37.2 (C-2_a), 24.6 (C(O)CH_3), 23.9 (C-3), 22.9 (C-2), 18.1 (C-6). HRMS (ESI) calcd for (M+Na) $C_{22}H_{25}N_3O_4Na$: 418.1743, found: 418.1737.



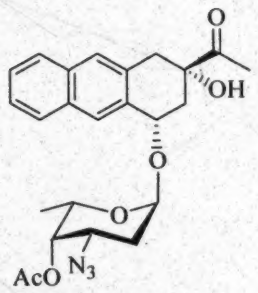
2.68

(1*S*,3*S*)-1-*O*-(4-*O*-acetyl-3-azido-2,3,6-deoxy-α-L-*arabino*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (2.68). Yield 31%. R_f 0.30 (3:1, hexanes-EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 7.78-7.84 (m, 3 H, Ar), 7.65 (s, 1 H, Ar), 7.40-7.55 (m, 2 H, Ar), 5.10 (app t, 1 H, $J_{1,2ax} = J_{1,2eq}$ = 3.6 Hz, H-1$_a$), 5.02 (d, 1 H, $J_{1,2ax}$ = 3.9 Hz, H-1), 4.74 (dd, 1 H, $J_{4,5} = J_{3,4}$ = 9.8 Hz, H-4), 4.44 (s, 1 H, 3°-OH), 3.88-4.00 (m, 2 H, H-3, H-5), 3.30 (d, 1 H, $J_{4ax,4eq}$ = 16.9 Hz, H-4$_a$ax), 3.24 (d, 1 H, $J_{4ax,4eq}$ = 16.9 Hz, H-4$_a$eq), 2.28-2.43 (m, 2 H, H-2$_a$ax, H-2$_a$eq), 2.26 (s, 3 H, C(O)CH_3), 2.16 (s, 3 H, OC(O)CH_3), 2.00 (ddd, 1 H, $J_{2ax,2eq} = J_{2ax,3}$ = 13.6 Hz, $J_{1,2ax}$ = 3.9 Hz, H-2ax), 1.81 (dd, 1 H, $J_{2ax,2eq}$ = 13.6 Hz, $J_{2eq,3}$ = 4.0 Hz, H-2eq), 1.25 (d, 3 H, $J_{5,6}$ = 6.3 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 211.4 (C=O), 169.9 (O*C*(O)CH_3), 133.7 (Ar), 131.7 (Ar), 131.6 (Ar), 130.6 (Ar), 128.4 (Ar), 128.1 (Ar), 127.8 (Ar), 127.1 (Ar), 126.7 (Ar), 125.9 (Ar), 92.9 (C-1), 78.0 (C-3$_a$), 75.4 (C-1$_a$), 71.9 (C-4), 66.6 (C-5), 57.4 (C-3), 39.2 (C-4$_a$), 37.7 (C-2$_a$), 34.9 (C-2), 24.4 (C(O)*C*H_3), 20.8 (OC(O)*C*H_3), 17.5 (C-6). HRMS (ESI) calcd for (M+Na) $C_{24}H_{27}N_3O_6Na$: 476.1798, found: 476.1793.



2.68β

(1*S*,3*S*)-1-*O*-(4-*O*-acetyl-3-azido-2,3,6-deoxy-β-L-*arabino*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (2.68β). Yield 19%. R_f 0.15 (3:1, hexanes-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$, δ_H) 7.95 (s, 1 H, Ar), 7.72-7.85 (m, 2 H, Ar), 7.60 (s, 1 H, Ar), 7.40-7.55 (m, 2 H, Ar), 5.30 (app t, 1 H, $J_{1,2ax} = J_{1,2eq} = 2.9$ Hz, H-1_a), 4.85 (dd, 1 H, $J_{1,2ax} = 9.6$ Hz, $J_{1,2eq} = 1.9$, H-1), 4.70 (dd, 1 H, $J_{4,5} = J_{3,4} = 9.5$ Hz, H-4), 4.00 (s, 1 H, 3°-OH), 3.42-3.62 (m, 2 H, H-3, H-5), 3.20 (s, 2 H, H-4_aax, H-4_aeq), 2.20-2.40 (m, 6 H, H-2ax, H-2_aax, H-2_aeq, *C*(O)CH_3), 2.15 (s, 3 H, OC(O)CH_3), 1.67-1.80 (m, 1 H, H-2eq), 1.30 (d, 3 H, $J_{5,6} = 6.1$ Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 212.3 (C=O), 169.9 (O*C*(O)CH_3), 133.7 (Ar), 131.7 (Ar), 131.6 (Ar), 130.6 (Ar), 128.4 (Ar), 128.1 (Ar), 127.8 (Ar), 127.1 (Ar), 126.7 (Ar), 125.9 (Ar), 96.5 (C-1), 77.8 (C-3_a), 74.8 (C-1_a), 72.5 (C-4), 71.1 (C-5), 59.8 (C-3), 39.0 (C-4_a), 36.3 (C-2_a), 34.0 (C-2), 24.7 (C(O)*C*H_3), 20.9 (OC(O)*C*H_3), 17.6 (C-6). HRMS (ESI) calcd for (M+Na) $C_{24}H_{27}N_3O_6Na$: 476.1798, found: 476.1791.

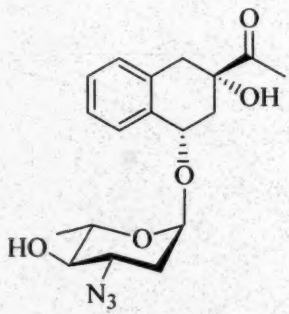


2.69

(1*S*,3*S*)-1-*O*-(4-*O*-acetyl-3-azido-2,3,6-deoxy-α-L-*lyxo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (2.69). Yield 57%. R_f 0.33 (3:1, hexanes-EtOAc); $[\alpha]_D$ -91.1 (*c* 0.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.77-7.85 (m, 3 H, Ar), 7.68 (s, 1 H, Ar), 7.45-7.53 (m, 2 H, Ar), 5.22-5.25 (m, 1 H, H-4), 5.15 (d, 1 H, $J_{1,2ax}$ = 4.0 Hz, H-1), 5.10 (app t, 1 H, $J_{1,2ax}$ = $J_{1,2eq}$ = 3.6 Hz, H-1_a), 4.43 (s, 1 H, 3°-OH), 4.16 (q, 1 H, $J_{5,6}$ = 6.6 Hz, H-5), 3.89 (ddd, 1 H, $J_{2ax,3}$ = 13.1 Hz, $J_{3,4}$ = 4.8 Hz, $J_{2eq,3}$ = 4.0 Hz, H-3), 3.29 (d, 1 H, $J_{4ax,4eq}$ = 16.6 Hz, H-4_aax), 3.24 (d, 1 H, $J_{4ax,4eq}$ = 16.6 Hz, H-4_aeq), 2.39 (dd, 1 H, $J_{2ax,2eq}$ = 14.8 Hz, $J_{1,2ax}$ = 3.6 Hz, H-2_aax), 2.30 (dd, 1 H, $J_{2ax,2eq}$ = 14.8 Hz, $J_{1,2eq}$ = 3.6 Hz, H-2_aeq), 2.25 (s, 3 H, C(O)CH_3), 2.19 (s, 3 H, OC(O)CH_3), 2.05 (ddd, 1 H, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 13.1 Hz, $J_{1,2ax}$ = 4.0 Hz, H-2ax), 1.78 (dd, 1 H, $J_{2ax,2eq}$ = 13.1 Hz, $J_{2eq,3}$ = 4.0 Hz, H-2eq), 1.27 (d, 3 H, $J_{5,6}$ = 6.6 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 211.5 (C=O), 170.5 (O*C*(O)CH_3), 133.8 (Ar), 131.8 (2 x Ar), 130.7 (Ar), 128.6 (Ar), 128.2 (Ar), 127.9 (Ar), 127.2 (Ar), 126.8 (Ar), 126.0 (Ar), 93.7 (C-1), 78.1 (C-3_a), 72.2 (C-1_a), 70.0 (C-4), 65.9 (C-5), 54.4 (C-3), 39.3 (C-4_a), 37.8 (C-2_a), 29.4 (C-2), 24.5 (C(O)*C*H_3), 20.7 (OC(O)*C*H_3), 16.9 (C-6). HRMS (ESI) calcd for (M+Na) $C_{24}H_{27}N_3O_6Na$: 476.1798, found: 476.1792.

3.5.2. General Procedure for the Removal of Acetate Group for 1,2,3,4-Tetrahydro-naphthyl and 1,2,3,4-Tetrahydro-anthranyl Glycosides.

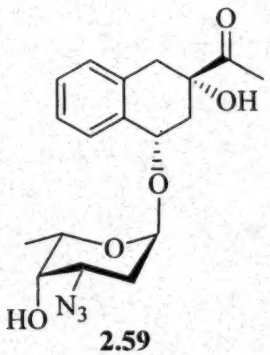
Protected glycosides (0.47 mmol) were dissolved in dry CH_3OH (5 mL) and K_2CO_3 (0.065 g, 0.47 mmol) was added. The mixture was stirred for 24 h, concentrated, and purified via column chromatography to afford the desired products.



2.58

(1*S*,3*S*)-1-*O*-(3-azido-2,3,6-deoxy-α-L-*arabino*-hexopyranosyl)-3-acetyl-3-hydroxyl-1, 2,3,4-tetrahydro-naphthalene (2.58). Yield 70%. R_f 0.38 (3:1, hexanes-EtOAc); $[\alpha]_D$ -74.6 (*c* 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 7.19-7.38 (m, 4 H, Ar), 5.03 (d, 1 H, $J_{1,2ax}$ = 3.5 Hz, H-1), 4.90 (app t, 1 H, $J_{1,2ax} = J_{1,2eq}$ = 3.5 Hz, H-1_a), 4.54 (br s, 1 H, 2°-OH), 3.68-3.83 (m, 2 H, H-3, H-5), 3.13-3.21 (m, 2 H, H-4, H-4_aax), 3.01 (d, 1 H, $J_{4ax,4eq}$ = 17.2 Hz, H-4_aeq), 2.33 (s, 3 H, $C(O)CH_3$), 2.23-2.27 (m, 2 H, H-2_aax, H-2_aeq), 2.00 (m, 1 H, H-2eq), 1.69 (ddd, 1 H, $J_{2ax,2eq} = J_{2ax,3}$ = 12.9 Hz, $J_{1,2ax}$ = 3.5 Hz, H-2ax), 1.34 (d, 3 H, $J_{5,6}$ = 6.2 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 212.1 (C=O), 133.9

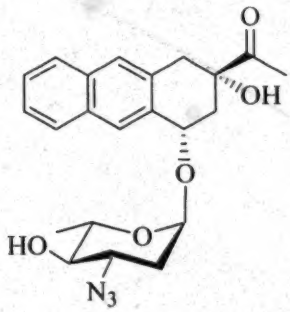
(Ar), 131.8 (Ar), 130.0 (Ar), 129.9 (Ar), 129.2 (Ar), 126.1 (Ar), 93.6 (C-1), 78.0 (C-3_a), 75.9 (C-1_a), 71.4 (C-4), 68.4 (C-5), 60.0 (C-3), 38.8 (C-4_a), 36.1 (C-2_a), 34.8 (C-2), 24.6 (C(O)CH_3), 17.7 (C-6). HRMS (ESI) calcd for (M+Na) $C_{18}H_{23}N_3O_5Na$: 384.1535, found: 384.1531.



2.59

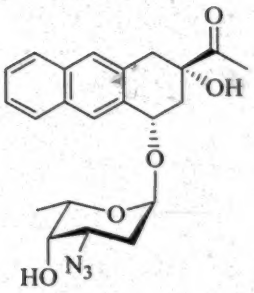
(1*S*,3*S*)-1-*O*-(3-azido-2,3,6-deoxy-α-L-*lyxo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (2.59). Yield 91%. R_f 0.31 (3:1, hexanes-EtOAc); $[\alpha]_D$ –114.7 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 7.18-7.37 (m, 4 H, Ar), 5.13 (d, 1 H, $J_{1,2ax}$ = 4.0 Hz, H-1), 4.90 (app t, 1 H, $J_{1,2ax}$ = $J_{1,2eq}$ = 3.4 Hz, H-1_a), 4.50 (s, 1 H, 2°-OH), 4.01 (q, 1 H, $J_{5,6}$ = 6.6 Hz, H-5), 3.70-3.80 (m, 2 H, H-3, H-4), 3.15 (d, 1 H, $J_{4ax,4eq}$ = 17.0 Hz, H-4_aax), 3.02 (d, 1 H, $J_{4ax,4eq}$ = 17.0 Hz, H-4_aeq), 2.32 (s, 3 H, C(O)CH_3), 2.22-2.26 (m, 2 H, H-2_aax, H-2_aeq), 2.06 (ddd, 1 H, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 13.0 Hz, $J_{1,2ax}$ = 4.0 Hz, H-2ax), 1.75 (dd, 1 H, $J_{2ax,2eq}$ = 13.0 Hz, $J_{2eq,3}$ = 4.0 Hz, H-2eq), 1.33 (d, 3 H, $J_{5,6}$ = 6.6 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 211.9 (C=O), 133.7 (Ar), 131.8 (Ar), 129.9 (Ar), 129.2 (Ar), 129.1 (Ar), 126.2 (Ar), 94.4 (C-1), 77.9 (C-3_a), 71.9 (C-1_a), 69.4 (C-4), 66.6 (C-5), 56.6 (C-3), 38.9 (C-4_a), 36.1 (C-2_a), 28.4 (C-2), 24.6 (C(O)CH_3),

16.7 (C-6). HRMS (ESI) calcd for (M+Na) $C_{18}H_{23}N_3O_5Na$: 384.1535, found: 384.1530.



2.70

(1*S*,3*S*)-1-*O*-(3-azido-2,3,6-deoxy-α-L-*arabino*-hexopyranosyl)-3-acetyl-3-hydroxy-1, 2,3,4-tetrahydro-anthracene (2.70). Yield 60%. R_f 0.30 (1:1, hexanes-EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 7.78-7.84 (m, 3 H, Ar), 7.65 (s, 1 H, Ar), 7.40-7.55 (m, 2 H, Ar), 5.10 (app t, 1 H, $J_{1,2ax} = J_{1,2eq} = 3.5$ Hz, H-1_a), 5.02 (d, 1 H, $J_{1,2ax} = 3.5$ Hz, H-1), 4.50 (br s, 1 H, 2°-OH), 3.63-3.85 (m, 2 H, H-3, H-5), 3.28-3.33 (m, 2 H, H-4_aax, H-4_aeq), 3.20 (dd, 1 H, $J_{4,5} = J_{3,4} = 9.5$ Hz, H-4), 2.20-2.39 (m, 5 H, H-2_aax, H-2_aeq, C(O)CH_3), 2.00 (m, 1 H, H-2ax), 1.70-1.78 (m, 1 H, H-2eq), 1.40 (d, 3 H, $J_{5,6} = 6.2$ Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 211.7 (C=O), 133.7 (Ar), 131.7 (Ar), 131.6 (Ar), 130.6 (Ar), 128.5 (Ar), 128.2 (Ar), 127.8 (Ar), 127.1 (Ar), 126.6 (Ar), 125.8 (Ar), 92.9 (C-1), 78.1 (C-3_a), 76.6 (C-1_a), 71.6 (C-4), 68.4 (C-5), 60.0 (C-3), 39.2 (C-4_a), 37.5 (C-2_a), 34.7 (C-2), 24.5 (C(O)CH_3), 17.8 (C-6). HRMS (ESI) calcd for (M+Na) $C_{22}H_{25}N_3O_5Na$: 434.1692, found: 434.1688.

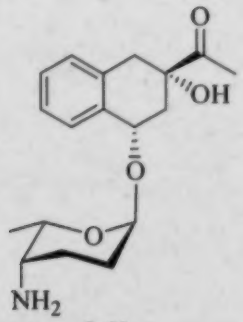


2.71

(1*S*,3*S*)-1-*O*-(3-azido-2,3,6-deoxy-α-L-*lyxo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (2.71). Yield 61%. R_f 0.34 (1:1, hexanes-EtOAc); $[\alpha]_D$ –55.4 (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 7.77-7.86 (m, 3 H, Ar), 7.67 (s, 1 H, Ar), 7.45-7.52 (m, 2 H, Ar), 5.09-5.16 (m, 2 H, H-1_a, H-1), 4.50 (br s, 1 H, 2°-OH), 4.08 (q, 1 H, $J_{5,6}$ = 6.6 Hz, H-5), 3.82-3.87 (m, 1 H, H-3), 3.76 (s, 1 H, H-4), 3.37 (br s, 2 H, H-4_aax, H-4_aeq), 2.38 (dd, 1 H, $J_{2ax,2eq}$ = 14.7 Hz, $J_{1,2ax}$ = 3.9 Hz, H-2_aax), 2.26-2.32 (m, 4 H, H-2_aeq, C(O)CH_3), 2.05 (ddd, 1 H, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 12.7 Hz, $J_{1,2ax}$ = 3.9 Hz, H-2ax), 1.75 (dd, 1 H, $J_{2ax,2eq}$ = 12.7 Hz, $J_{2eq,3}$ = 3.9 Hz, H-2eq), 1.40 (d, 3 H, $J_{5,6}$ = 6.6 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 211.6 (C=O), 133.6 (Ar), 131.7 (Ar), 131.6 (Ar), 130.6 (Ar), 128.6 (Ar), 128.1 (Ar), 127.8 (Ar), 127.1 (Ar), 126.6 (Ar), 125.9 (Ar), 93.6 (C-1), 78.1 (C-3_a), 71.9 (C-1_a), 69.5 (C-4), 66.6 (C-5), 56.7 (C-3), 39.2 (C-4_a), 37.4 (C-2_a), 28.4 (C-2), 24.5 (C(O)CH_3), 16.8 (C-6). HRMS (ESI) calcd for (M+Na) $C_{22}H_{25}N_3O_5Na$: 434.1692, found: 434.1686.

3.5.3. General Procedure for the Reduction of 1,2,3,4-Tetrahydro-naphthyl and 1,2,3,4-Tetrahydro-anthranyl Azido Glycosides.

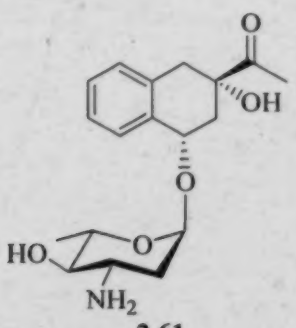
Azido glycosides (0.3 mmol) and triphenylphosphine (0.6 mmol) were dissolved in a solution of THF (10 mL) and water (1 mL) and the reaction mixture was stirred for 3-12 h at 55 °C. Concentration, followed by purification by column chromatography afforded the desired products.



2.60

(1*S*,3*S*)-1-*O*-(4-amino-2,3,4,6-tetradeoxy-α-L-*threo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (2.60). Yield 85%. R_f 0.25 (10:1, CH_2Cl_2-CH_3OH); $[\alpha]_D$ -70.6 (*c* 0.5, CH_3OH); ^1H NMR (500 MHz, CD_3OD, δ_H) 7.20-7.35 (m, 4 H, Ar), 5.18 (d, 1 H, $J_{1,2ax}$ = 3.3 Hz, H-1), 4.83 (app t, 1 H, $J_{1,2ax} = J_{1,2eq}$ = 5.8 Hz, H-1_a), 4.78 (s, 1 H, 3°-OH), 4.30-4.40 (m, 1 H, H-5), 3.35 (br s, 1 H, H-4), 3.10 (d, 1 H, $J_{4ax,4eq}$ = 16.0 Hz, H-4_aax), 2.93 (d, 1 H, $J_{4ax,4eq}$ = 16.0 Hz, H-4_aeq), 2.50 (dd, 1 H, $J_{2ax,2eq}$ = 13.6 Hz, $J_{1,2eq}$ = 5.8 Hz, H-2_aax), 2.25-2.32 (m, 1 H, H-3eq), 2.26 (s, 3 H, C(O)CH_3), 2.17 (dd, 1 H, $J_{2ax,2eq}$ = 13.6 Hz, $J_{1,2eq}$ = 5.8 Hz, H-2_aeq), 1.82-1.92 (m, 2 H, H-3ax,

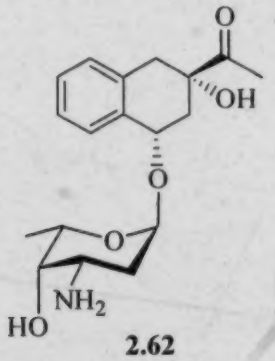
H-2ax), 1.65-1.72 (m, 1 H, H-2eq), 1.24 (d, 3 H, $J_{5,6}$ = 6.8 Hz, H-6); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 213.4 (C=O), 136.7 (Ar), 135.3 (Ar), 130.0 (Ar), 129.2 (Ar), 128.8 (Ar), 127.4 (Ar), 98.4 (C-1), 78.8 (C-3_a), 75.4 (C-1_a), 65.0 (C-5), 50.5 (C-4), 48.5 (C-4_a), 40.1 (C-2_a), 39.7 (C-3), 24.3 (C(O)CH_3), 23.4 (C-2), 17.5 (C-6). HRMS (ESI) calcd for (M+H) $C_{18}H_{26}NO_4$: 320.1862, found: 320.1877.



2.61

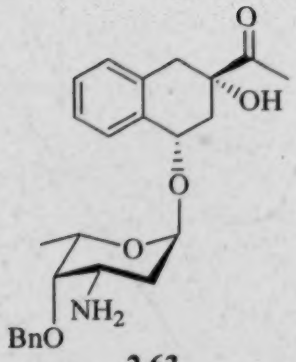
(1*S*,3*S*)-1-*O*-(3-amino-2,3,6-deoxy-α-L-*arabino*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (2.61). Yield 65%. R_f 0.18 (10:1, CH_2Cl_2-CH_3OH); ^{1}H NMR (500 MHz, CD_3OD, δ_H) 7.19-7.38 (m, 4 H, Ar), 5.11 (d, 1 H, $J_{1,2ax}$ = 3.8 Hz, H-1), 4.82 (app t, 1 H, $J_{1,2ax}$ = $J_{1,2eq}$ = 5.1 Hz, H-1_a), 3.84-3.90 (m, 1 H, H-5), 3.37-3.45 (m, 1 H, H-3), 3.08-3.18 (m, 2 H, H-4, H-4_aax), 2.93 (d, 1 H, $J_{4ax,4eq}$ = 16.2 Hz, H-4_aeq), 2.50 (dd, 1 H, $J_{2ax,2eq}$ = 14.0 Hz, $J_{1,2ax}$ = 5.1 Hz, H-2_aax), 2.22 (s, 3 H, C(O)CH_3), 2.16-2.22 (m, 1 H, H-2eq), 2.05 (dd, 1 H, $J_{2ax,2eq}$ = 14.0 Hz, $J_{1,2eq}$ = 5.1 Hz, H-2_aeq), 1.82 (ddd, 1 H, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 12.8 Hz, $J_{1,2ax}$ = 3.8 Hz, H-2ax), 1.34 (d, 3 H, $J_{5,6}$ = 6.3 Hz, H-6); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 213.2 (C=O), 136.5 (Ar), 135.4

(Ar), 130.1 (Ar), 129.3 (Ar), 128.9 (Ar), 127.4 (Ar), 97.3 (C-1), 78.8 (C-3_a), 75.3 (C-1_a), 75.0 (C-4), 70.2 (C-5), 51.4 (C-3), 48.5 (C-4_a), 40.2 (C-2_a), 39.6 (C-2), 24.3 (C(O)CH_3), 17.9 (C-6). HRMS (ESI) calcd for (M+H) $C_{18}H_{26}NO_5$: 336.1811, found: 336.1808.



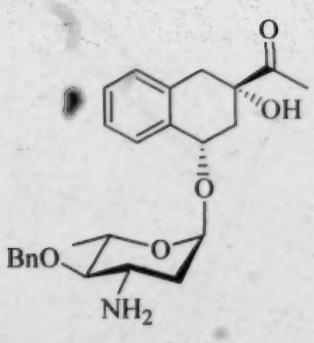
2.62

(1*S*,3*S*)-1-*O*-(3-amino-2,3,6-deoxy-α-L-*lyxo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (2.62). Yield 70%. R_f 0.15 (10:1, CH_2Cl_2-CH_3OH); $[\alpha]_D$ –120.3 (*c* 0.6, CH_3OH); ^1H NMR (400 MHz, CD_3OD, δ_H) 7.18-7.38 (m, 4 H, Ar), 5.16 (d, 1 H, $J_{1,2ax}$ = 3.1 Hz, H-1), 4.80-4.89 (m, 1 H, H-1_a), 4.13 (q, 1 H, $J_{5,6}$ = 6.7 Hz, H-5), 3.63-3.71 (m, 2 H, H-3, H-4), 3.10 (d, 1 H, $J_{4ax,4eq}$ = 16.1 Hz, H-4_aax), 2.91 (d, 1 H, $J_{4ax,4eq}$ = 16.1 Hz, H-4_aeq), 2.49 (m, 1 H, H-2_aeq), 2.23 (s, 3 H, C(O)CH_3), 1.98-2.09 (m, 2 H, H-2ax, H-2_aax), 1.83-1.90 (m, 1 H, H-2eq), 1.27 (d, 3 H, $J_{5,6}$ = 6.7 Hz, H-6); ^{13}C NMR (100 MHz, CD_3OD, δ_C) 213.4 (C=O), 136.6 (Ar), 135.3 (Ar), 130.1 (Ar), 130.0 (Ar), 129.3 (Ar), 127.4 (Ar), 97.9 (C-1), 78.8 (C-3_a), 75.4 (C-1_a), 68.0 (C-4), 67.8 (C-5), 48.5 (C-3), 40.0 (C-4_a), 39.6 (C-2_a), 29.8 (C-2), 24.4 (C(O)CH_3), 17.0 (C-6). HRMS (ESI) calcd for (M+H) $C_{18}H_{26}NO_5$: 336.1811, found: 336.1806.



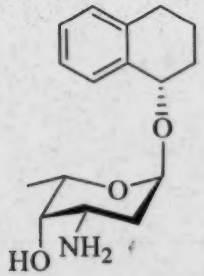
2.63

(1*S*,3*S*)-1-*O*-(3-amino-4-*O*-benzyl-2,3,6-deoxy-α-L-*lyxo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (2.63). Yield 63%. R_f 0.20 (20:1, CH_2Cl_2-CH_3OH); ^{1}H NMR (400 MHz, CD_3OD, δ_H) 7.10-7.40 (m, 9 H, Ar), 5.05 (d, 1 H, $J_{1,2ax}$ = 3.3 Hz, H-1), 4.90 (d, 1 H, J = 11.2 Hz, PhCH_2), 4.80-4.86 (m, 1 H, H-1$_a$) , 4.11 (q, 1 H, $J_{5,6}$ = 6.3 Hz, H-5), 4.63 (d, 1 H, J = 11.2 Hz, PhCH_2), 3.50-3.55 (m, 1 H, H-4), 3.20-3.38 (m, 1 H, H-3), 3.10 (d, 1 H, $J_{4ax,4eq}$ = 16.0 Hz, H-4$_a$ax), 2.89 (d, 1 H, $J_{4ax,4eq}$ = 16.0 Hz, H-4$_a$eq), 2.45 (dd, 1 H, $J_{2ax,2eq}$ = 13.8 Hz, $J_{1,2ax}$ = 6.1 Hz, H-2$_a$ax), 2.24 (s, 3 H, C(O)CH_3), 2.02 (dd, 1 H, $J_{2ax,2eq}$ = 13.8 Hz, $J_{1,2eq}$ = 6.1 Hz, H-2$_a$eq), 1.70-1.87 (m, 2 H, H-2ax, H-2eq), 1.27 (d, 3 H, $J_{5,6}$ = 6.3 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 213.4 (C=O), 145.8 (Ar), 139.8 (Ar), 136.7 (Ar), 135.2 (Ar), 130.1 (Ar), 130.0 (Ar), 129.5 (Ar), 129.3 (Ar), 129.2 (Ar), 129.1 (Ar), 128.9 (Ar), 127.3 (Ar), 98.9 (C-1), 80.7 (C-4), 78.9 (C-3$_a$), 77.1 (PhCH_2), 75.1 (C-1$_a$), 67.3 (C-5), 55.9 (C-3), 38.9 (C-4$_a$), 35.9 (C-2$_a$), 28.9 (C-2), 24.6 (C(O)CH_3), 17.8 (C-6). HRMS (ESI) calcd for (M+H) $C_{25}H_{32}NO_5$: 426.2281, found: 426.2275.



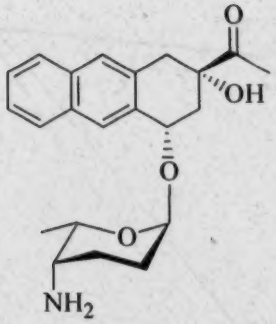
2.64

(1*S*,3*S*)-1-*O*-(3-amino-4-*O*-benzyl-2,3,6-deoxy-α-L-*arabino*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (2.64). Yield 32%. R_f 0.22 (20:1, CH_2Cl_2-CH_3OH); $[\alpha]_D$ -89.1 (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD, δ_H) 7.10-7.43 (m, 9 H, Ar), 5.05 (d, 1 H, $J_{1,2ax}$ = 3.3 Hz, H-1), 4.78-4.82 (m, 1 H, H-1_a), 4.74 (d, 1 H, *J* = 11.3 Hz, PhCH_2), 4.71 (d, 1 H, *J* = 11.3 Hz, PhCH_2), 3.85-3.94 (m, 1 H, H-5), 3.13-3.22 (m, 1 H, H-3), 3.10 (d, 1 H, $J_{4ax,4eq}$ = 15.9 Hz, H-4_aax), 2.96 (dd, 1 H, $J_{3,4} = J_{4,5}$ 9.4 Hz, H-4), 2.90 (d, 1 H, $J_{4ax,4eq}$ = 15.9 Hz, H-4_aeq), 2.48 (dd, 1 H, $J_{2ax,2eq}$ = 13.9 Hz, $J_{1,2ax}$ = 5.5 Hz, H-2_aax), 2.24 (s, 3 H, C(O)CH_3), 2.00-2.09 (m, 2 H, H-2eq, H-2_aeq), 1.64 (ddd, 1 H, $J_{2ax,2eq} = J_{2ax,3}$ = 12.5Hz, $J_{1,2ax}$ = 3.3 Hz, H-2ax), 1.33 (d, 3 H, $J_{5,6}$ = 6.3 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 212.3 (C=O), 137.4 (Ar), 134.1 (Ar), 131.7 (Ar), 130.1 (Ar), 130.0 (Ar), 129.3 (Ar), 128.6 (2 x Ar), 128.4 (2 x Ar), 128.1 (Ar), 126.1 (Ar), 93.3 (C-1), 83.8 (C-4), 78.1 (C-3_a), 75.4 (PhCH_2), 71.2 (C-1_a), 68.2 (C-5), 53.5 (C-3), 39.0 (C-4_a), 36.2 (C-2_a), 35.5 (C-2), 24.8 (C(O)CH_3), 18.2 (C-6). HRMS (ESI) calcd for (M+H) $C_{25}H_{32}NO_5$: 426.2281, found: 426.2277.



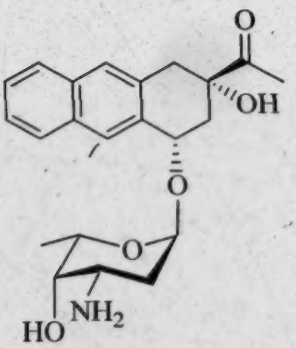
2.66

(1*S*)-1-*O*-(3-amino-2,3,6-deoxy-α-L-*lyxo*-hexopyranosyl)-1,2,3,4- tetrahydro-naphthalene (2.66). Yield 90%. R_f 0.17 (10:1, CH_2Cl_2-CH_3OH); ^1H NMR (500 MHz, CD_3OD, δ_H) 7.04-7.29 (m, 4 H, Ar), 5.11 (d, 1 H, $J_{1,2ax}$ = 3.3 Hz, H-1), 4.64 (app t, 1 H, $J_{1,2ax} = J_{1,2eq}$ = 4.2 Hz, H-1_a), 4.02 (q, 1 H, $J_{5,6}$ = 6.5 Hz, H-5), 3.23 (ddd, $J_{2ax,3}$ = 12.5 Hz, $J_{3,4}$ = 4.6 Hz, $J_{2eq,3}$ = 2.9 Hz, 1 H, H-3), 3.44 (s, 1 H, H-4), 2.65-2.84 (m, 2 H, H-4_aax, H-4_aeq), 1.65-2.05 (m, 6 H, H-2ax, H-2eq, H-2_aax, H-2_aeq, H-3_aax, H-3_aeq), 1.24 (d, 3 H, $J_{5,6}$ = 6.5 Hz, H-6); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 138.7 (Ar), 137.5 (Ar), 130.4 (Ar), 130.0 (Ar), 128.7 (Ar), 126.5 (Ar), 98.3 (C-1), 75.4 (C-1_a), 71.1 (C-4), 68.2 (C-5), 48.1 (C-3), 33.1 (C-4_a), 31.3 (C-2_a + C-3_a), 29.8 (C-2), 17.3 (C-6). HRMS (ESI) calcd for (M+H) $C_{16}H_{24}NO_3$: 278.1756, found: 278.1754.



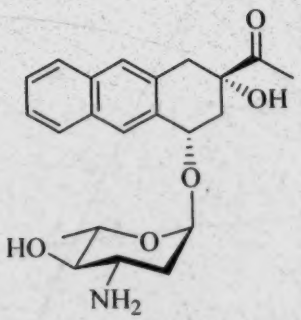
2.72

(1*S*,3*S*)-1-*O*-(4-amino-2,3,4,6-tetradeoxy-α-L-*threo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (2.72). Yield 43%. R_f 0.13 (10:1, CH_2Cl_2-CH_3OH); $[\alpha]_D$ -88.9 (*c* 0.2, $CHCl_3$); ^1H NMR (500 MHz, CD_3OD, δ_H) 7.74-7.83 (m, 3 H, Ar), 7.63 (s, 1 H, Ar), 7.39-7.45 (m, 2 H, Ar), 4.95-5.00 (m, 2 H, H-1, H-1_a), 4.20-4.30 (m, 1 H, H-5), 3.21 (d, 1 H, $J_{4ax,4eq}$ = 15.5 Hz, H-4_aax), 3.11 (d, 1 H, $J_{4ax,4eq}$ = 15.5 Hz, H-4_aeq), 2.80 (br s, 1 H, H-4), 2.50 (dd, 1 H, $J_{2ax,2eq}$ = 14.1 Hz, $J_{1,2ax}$ = 6.1 Hz, H-2_aax), 2.28 (s, 3 H, C(O)CH_3), 2.16 (ddd, 1 H, $J_{3ax,3eq}$ = $J_{2ax,3ax}$ = 13.9 Hz, $J_{3ax,4}$ = 4.4 Hz, H-3ax), 2.03 (dd, 1 H, $J_{2ax,2eq}$ = 13.9 Hz, $J_{1,2eq}$ = 6.1 Hz, H-2_aeq), 1.93 (ddd, 1 H, $J_{2ax,2eq}$ = $J_{2ax,3ax}$ = 13.9 Hz, $J_{2ax,3eq}$ = 4.3 Hz, H-2ax), 1.64-1.68 (m, 1 H, H-3eq), 1.56-1.61 (m, 1 H, H-2eq), 1.20 (d, 3 H, $J_{5,6}$ = 6.7 Hz, H-6); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 213.7 (C=O), 136.0 (Ar), 134.8 (Ar), 133.8 (Ar), 133.7 (Ar), 128.9 (Ar), 128.8 (Ar), 128.2 (Ar), 128.1 (Ar), 127.1 (Ar), 126.6 (Ar), 97.7 (C-1), 79.4 (C-3_a), 74.3 (C-1_a), 67.7 (C-5), 49.6 (C-4), 41.0 (C-4_a), 39.8 (C-2_a), 39.8 (C-3), 26.6 (C-2), 24.6 (C(O)CH_3), 17.8 (C-6). HRMS (ESI) calcd for (M+H) $C_{22}H_{28}NO_4$: 370.2018, found: 370.2013.



2.73

(1*S*,3*S*)-1-*O*-(3-amino-2,3,6-deoxy-α-L-*lyxo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (2.73). Yield 40%. R_f 0.15 (10:1, CH_2Cl_2-CH_3OH); ^1H NMR (400 MHz, CD_3OD, δ_H) 7.72-7.84 (m, 3 H, Ar), 7.61 (s, 1 H, Ar), 7.37-7.46 (m, 2 H, Ar), 5.04 (br s, 1 H, H-1), 4.96 (app t, 1 H, $J_{1,2ax} = J_{1,2eq} = 5.9$ Hz, H-1_a), 4.80 (s, 1 H, 2°-OH), 4.11 (q, 1 H, $J_{5,6} = 6.5$ Hz, H-5), 3.50-3.55 (m, 1 H, H-3), 3.28-3.36 (m, 1 H, H-4), 3.20 (d, 1 H, $J_{4ax,4eq} = 15.7$ Hz, H-4_aax), 3.11 (d, 1 H, $J_{4ax,4eq} = 15.7$ Hz, H-4_aeq), 2.60 (dd, 1 H, $J_{2ax,2eq} = 14.2$ Hz, $J_{1,2ax} = 5.9$ Hz, H-2_aax), 2.24 (s, 3 H, C(O)CH_3), 2.01 (dd, 1 H, $J_{2ax,2eq} = 14.2$ Hz, $J_{1,2eq} = 5.9$ Hz, H-2_aeq), 1.76-1.86 (m, 2 H, H-2ax, H-2eq), 1.28 (d, 3 H, $J_{5,6} = 6.5$ Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 213.4 (C=O), 135.6 (Ar), 134.6 (Ar), 133.7 (Ar), 133.5 (Ar), 128.7 (Ar), 128.0 (Ar), 127.9 (Ar), 126.9 (Ar), 126.6 (Ar), 126.5 (Ar), 97.6 (C-1), 74.4 (C-3_a), 71.9 (C-1_a), 71.1 (C-4), 68.3 (C-5), 48.2 (C-3), 47.8 (C-4_a), 40.8 (C-2_a), 39.6 (C-2), 32.8 (C(O)CH_3), 17.1 (C-6). HRMS (ESI) calcd for (M+H) $C_{22}H_{28}NO_5$: 386.1967, found: 386.1962.



2.74

(1*S*,3*S*)-1-*O*-(3-amino-2,3,6-deoxy-α-L-*arabino*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (2.74). Yield 45%. R_f 0.15 (10:1, CH_2Cl_2-CH_3OH); ^{1}H NMR (600 MHz, CD_3OD, δ_H) 7.74-7.84 (m, 3 H, Ar), 7.64 (s, 1 H, Ar), 7.39-7.46 (m, 2 H, Ar), 5.03 (d, 1 H, $J_{1,2ax}$ = 3.5 Hz, H-1), 4.98 (app t, 1 H, $J_{1,2ax}$ = $J_{1,2eq}$ = 5.6 Hz, H-1$_a$), 3.87 (dq, 1 H, $J_{4,5}$ = 9.7 Hz, $J_{5,6}$ = 6.6 Hz, H-5), 3.30-3.35 (m, 1 H, H-3), 3.22 (d, 1 H, $J_{4ax,4eq}$ = 15.3 Hz, H-4$_a$ax), 3.13 (d, 1 H, $J_{4ax,4eq}$ = 15.3 Hz, H-4$_a$eq), 3.05 (dd, 1 H, $J_{4,5}$ = $J_{3,4}$ = 9.7 Hz, H-4), 2.63 (dd, 1 H, $J_{2ax,2eq}$ = 14.2 Hz, $J_{1,2ax}$ = 5.6 Hz, H-2$_a$ax), 2.16 (ddd, 1 H, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 12.4 Hz, $J_{1,2ax}$ = 3.5 Hz, H-2ax), 2.03 (dd, 1 H, $J_{2ax,2eq}$ = 14.2 Hz, $J_{1,2eq}$ = 5.6 Hz, H-2$_a$eq), 1.74 (dd, $J_{2ax,2eq}$ = 12.4 Hz, $J_{2eq,3}$ = 3.4 Hz, H-2eq), 1.34 (d, 3 H, $J_{5,6}$ = 6.6 Hz, H-6); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 213.4 (C=O), 135.6 (Ar), 134.8 (Ar), 133.9 (Ar), 133.7 (Ar), 128.8 (Ar), 128.3 (Ar), 128.2 (Ar), 127.2 (Ar), 126.8 (Ar), 126.7 (Ar), 96.7 (C-1), 79.3 (C-3$_a$), 76.7 (C-1$_a$), 74.7 (C-4), 70.2 (C-5), 48.9 (C-3), 39.2 (C-4$_a$), 41.1 (C-2$_a$), 39.7 (C-2), 24.4 (C(O)CH_3), 18.0 (C-6). HRMS (ESI) calcd for (M+H) $C_{22}H_{28}NO_5$: 386.1967, found: 386.1963.

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